CIMETIDINE IN PEPTIC ULCER DISEASE

HENK FESTEN

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Short and long term treatment and studies
on immunological effects

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PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE KATHOLIEKE UNIVERSITEIT TE NIJMEGEN, OP GEZAG VAN DE RECTOR MAGNIFICUS PROF. DR. P. G. A. B. WIJDEVELD VOLGENS HET BESLUIT VAN HET COLLEGE VAN DECANEN IN HET OPENBAAR TE VERDEDIGEN OP 20 JUNI 1980 DES NAMIDDAGS TE 4 UUR

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Voor dit onderzoek werd steun ontvangen uit het onderzoekfonds voor arts-assistenten van de medische faculteit te Nijmegen.

CONTENTS

CHAPTER 1

INTRODUCTION AND OUTLINE OF INVESTIGATIONS

Introduction

The pathogenesis of peptic ulcer is believed to be multifactorial but its aetiology has not been fully established.Several of the factors contributing to the development of peptic ulcers have been studied (1). A key role has always been attributed to gastric acid. In 1910 Schwartz postulated that without the presence of gastric acid no peptic ulcer can develop and his dictum: "no acid no ulcer" has withstood the ravages of time (2).

Gastric acid is produced by the parietal cells in corpus and fundus of the stomach. Three substances in the body are known to be capable of stimulating the parietal cells to produce hydrochloric acid. These are acetylcholine, gastrin and histamine. The parietal cells probably have three different receptors for each of these 3 substances (3). The 3 receptors interact with each other:a threshold stimulation by one greatly enhances the responses to the 2 other stimuli, and blockade of one of these receptors concomitantly blocks the effects of stimulation on the others (4). Acetylcholine and gastrin are known to play important physiological roles. Acetylcholine is liberated from the parietal cell after vagal stimulation. The hormone gastrin is secreted by gastrin producing cells in the antral and duodenal mucosa in response to several stimuli. Gastrin reaches the parietal cells via the bloodstream. Until recently the physiologic role of histamine in gastric acid secretion has been disputed.

Histamine is formed by decarboxylation of histamine (fig 1). Histamine is present in large amounts in most body tissues including the gastric mucosa (5). Its main effects have been reported in a number of papers by Dale and Laidlaw: histamine causes contraction of smooth muscle in bronchi, ileum and arteries,it increases the heart rate and inhibits uterine contractions (6). The gastric acid stimulatory effect of histamine was later discovered by Popielsky (7). The first substances which were able to antagonize histamine were described by Bovet and Staub (8). Surprisingly, these classical antihistamines did not inhibit all effects of histamine. They had, for instance, no effect on the gastric acid stimulatory capacity of histamine. In 1966, Ash and Schild defined the effects of histamine antagonized by the conventional antihistamines as mediated through H_1-receptors, and those who were not by H_2-receptors (9).

The classical antihistamines shared the side-chain with histamine while the imidazole ring was modified (fig 1). Black and co-workers succeeded in synthesizing specific H_2-receptor blocking compounds by modifying the side-chain

of the histamine molecule leaving the imidazole ring intact (10) (fig 1).

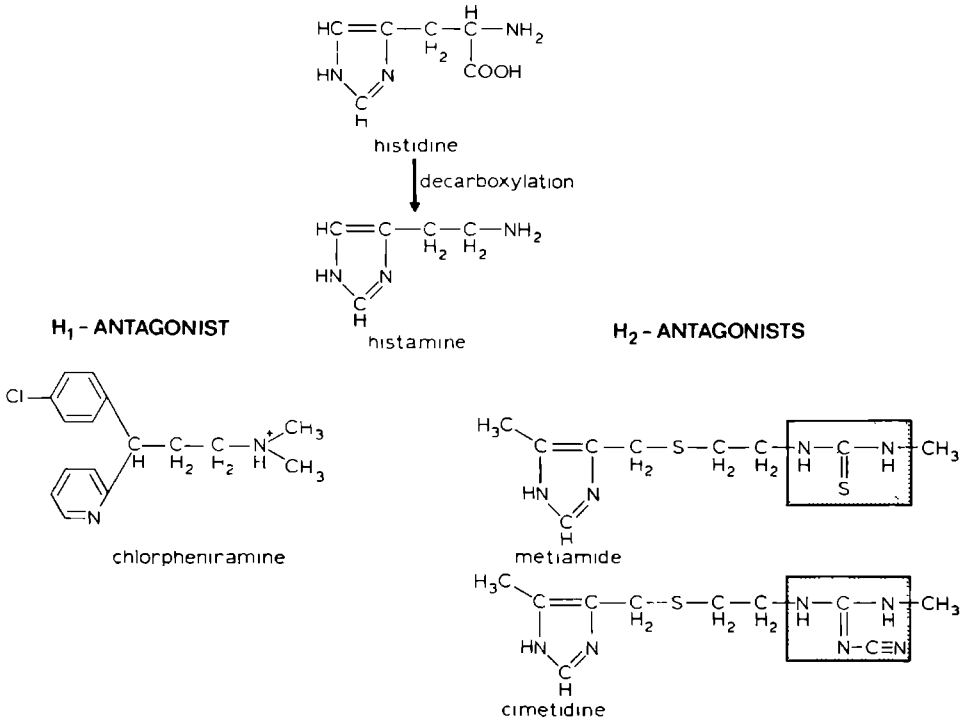

Fig 1 The formation of histamine by decarboxylation of histidine and some examples of H_1- and H_2-receptor blocking agents. The shaded area in the metiamide formula represents the thiourea moiety and in the cimetidine formula the cyanoguanidine group.

In a recent article 2 key members of this team describe the long and laborious road they had to go before their goal was achieved (11). From 1964 to 1970 some 700 compounds had been synthesized and tested before burimamide, the first competitive antagonist of histamine on H_2-receptors,was discovered. The effect of burimamide was weak and it was not active orally (10). Metiamide the second H_2-receptor antagonist was a potent inhibitor of gastric acid secretion and was well absorbed from the gut (12). It caused, however, agranulocytosis in a number of cases and therefore it was withdrawn (13). This complication is attributed to the thiourea group of the side-chain. In the third H_2-receptor antagonist this group has been substituted by a cyanoguanidine group (14) (fig 1). This new compound, cimetidine, proved to be a

potent inhibitor of gastric acid secretion, provoked by all known stimuli (15).

All therapies for peptic ulcer disease have been directed towards a reduction of gastric acid. Surgical treatment reduces gastric acid by cutting the vagal nerves (vagotomy) or removing the gastrin producing cells (antrectomy). In medical treatment often antacids and/or anticholinergics are prescribed. Antacids reduce intragastric acidity by buffering intraluminal gastric acid. To achieve ulcer healing, however, frequent and high doses are required (16). Anticholinergics inhibit vagally stimulated gastric acid secretion. In effective doses, however, they produce side effects and a favourable effect of anticholinergics on ulcer healing has not been proven (17).

Therefore this new drug, cimetidine, capable of inhibiting gastric acid secretion without these disadvantages, was very promising. It offered the prospect of a more effective medical treatment for peptic ulcer and thus possibly a decrease in the necessity for surgical procedures.

Outline of investigations

The aim of this study was to investigate the usefulness of treatment with cimetidine in peptic ulcer disease.
Firstly, the effect of cimetidine on gastric acid secretion was examined (chapter 2). Thereafter the role of cimetidine in the treatment of various acid peptic diseases was established: in duodenal and gastric ulcer (chapter 2), and in recurrent ulcer after partial gastrectomy (chapter 3). In reflux oesophagitis gastric acid is also believed to play an important role. Results of treatment of this condition with cimetidine are given in chapter 4. In the Zollinger-Ellison syndrome hypersecretion of gastric acid with all its consequences is caused by hypergastrinaemia originating from a gastrin producing tumor. Short and long term treatment of these patients with cimetidine was studied (chapter 5). The effect of long term treatment with cimetidine on gastric acid secretion, serum gastrin, the blood cimetidine levels and the acid inhibitory effect of cimetidine is presented in chapter 6. In chapter 7 the intra- and interindividual variability of blood concentration of cimetidine after an oral gift was studied. Retrospectively these concentrations were related to the clinical effect of treatment with cimetidine in patients with peptic ulcer.

As H_2-receptors are also present on T lymphocytes (18), possible immunological effects of treatment with cimetidine were studied in man (chapter 8)

and in a transplantation model of inbred mice (chapter 9).

Finally a review of the literature on the clinical use of cimetidine is presented in chapter 10.

References

1 ISENBERG J, RICHARDSON CT, FORDTRAN JS: Pathogenesis of peptic ulcer. In: Gastrointestinal disease. Edited by M Sleisenger and J Fordtran. Philadelphia, London, Toronto. WB Saunders Company 1978, p 792

2 SCHWARTZ K: Ueber penetrierende Magen- und Jejunalgeschwüre. Beitr Klin Chir 67: 96, 1910

3 GROSSMAN MI, KONTUREK SJ: Inhibition of acid secretion in dog by metiamide, a histamine antagonist acting on H_2-receptors. Gastroenterology 66: 517, 1974

4 SOLL AH: Interaction of histamine with gastrin and carbamylcholine on oxygen uptake by isolated mammalian parietal cells. J Clin Invest 61: 381, 1978

5 KAHLSON G, ROSENGREN E: New approaches to the physiology of histamine. Physiol Rev 48: 155, 1968

6 DALE HH, LAIDLAW PP: The physiological action of B-imidazolylethylamine. J Physiol (Lond) 41: 318, 1910

7 POPIELSKI L: B-Imidazolyläthylamin und die Organextrakte. Erster Teil: B-Imidazolyläthylamin als mächtiger Erreger der Magendrüsen. Pflügers Arch des Physiol 178: 214, 1920

8 BOVET D, STAUB AM: Action protectrice des éthers phénolique au cours de l'intoxication histaminique. C r Soc Biol 124: 547, 1937

9 ASH ASF, SCHILD HO: Receptors mediating some actions of histamine. Br J Pharmacol 27: 427, 1966

10 BLACK JW, DUNCAN WAM, DURANT CJ et al: Definition and antagonism of histamine H_2-receptors. Nature 236: 385, 1972

11 DUNCAN WAM, PARSONS ME: Reminiscenses of the development of cimetidine. Gastroenterology 78: 620, 1980

12 WOOD CJ, SIMKINS MA: International symposium on histamine H_2-receptor antagonists. Research and development division, Smith Kline and French Laboratories Ltd, Welwyn Garden City 1973

13 FORREST JAH, SHEARMAN DJC, SPENCE R et al: Neutropenia associated with metiamide. Lancet 1: 392, 1975

14 BRIMBLECOMBE RW, DUNCAN WAM, DURANT GJ et al: Cimetidine, a non-thiourea H_2-receptor antagonist. J Int Med Res 3: 86, 1975

15 RICHARDSON CT: Effect of H_2-receptor antagonists on gastric acid secretion and serum gastrin concentration. A review. Gastroenterology 74: 366, 1978

16 PETERSON WL, STURDEVANT RAL, FRANKL HD et al: Healing of duodenal ulcer with an antacid regimen. N Engl J Med 297: 341, 1977

17 IVEY KJ: Anticholinergics: do they work in peptic ulcer? Gastroenterology 68: 154, 1975

18 PLAUT M, LICHTENSTEIN LM, HENNEY CS: Properties of a subpopulation of T cells bearing histamine receptors. J Clin Invest 55: 856, 1975

THE INHIBITION OF GASTRIC ACID SECRETION BY CIMETIDINE AND THE RESULTS OF A DOUBLE BLIND TRIAL OF CIMETIDINE IN THE TREATMENT OF PEPTIC ULCER DISEASE

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Abstract

A reduction in the basal as well as the pentagastrin stimulated gastric acid secretion was observed after administration of 200 mg cimetidine to 14 patients with a duodenal and 8 with a gastric ulcer. In a double blind study, the effect of cimetidine was compared to that of a placebo. In a group of 23 duodenal ulcer patients, 10 out of 12 patients treated with cimetidine showed healed ulcers after 4 weeks treatment, compared to 2 out of 11 patients treated with a placebo ($p<0.01$). Duodenal ulcer patients treated with cimetidine also exhibited a significant alleviation of ulcer symptoms.

Nine out of 13 gastric ulcer patients treated with cimetidine showed healing of the ulcer after 4 weeks and 4 out of 11 patients treated with a placebo (not significant). In gastric ulcer patients cimetidine as well as placebo achieved significant symptom relief.

Concerning side effects, some patients in the cimetidine group and to a lesser extent in the placebo group, exhibited a slight transient increase of the serum creatinine and SGPT levels.

Introduction

It has been shown that cimetidine effectively inhibits nocturnal (1,2) and meal stimulated (3-6) gastric acid secretion. Presently, cimetidine is extensively tested for the treatment of peptic ulcer disease (7-11).

This paper describes the reduction of gastric acid secretion using cimetidine, and the results of a double blind investigation of the effect of cimetidine in the treatment of peptic ulcers.

Patients and methods

Twenty-three patients with a duodenal and 24 with a gastric ulcer were studied. The ulcer was confirmed by endoscopy within one week before they entered the trial. Patients were treated as outpatients and were randomly, in double blind fashion, allocated to cimetidine 3 times daily, 200 mg after meals and 400 mg at bedtime, or matching placebo. All other ulcer medication was discarded and no diet was prescribed. Each patient was given a diary card to record ulcer symptoms day and night. Patients were seen at weekly intervals, at each visit they were asked for symptoms, side effects and diary cards were checked. Before the trial, after 2 weeks, and at the end of it, routine haematological and biochemical blood studies and urine analysis were performed (haemoglobin, haematocrit, red blood cell count, total

white blood cell count, differential and platelet count, creatinine, urea, uric acid, bilirubin, alkaline phosphatase, SGOT and SGPT). After 4 weeks treatment gastroscopy was repeated by an endoscopist who was not aware of the type of treatment of the patient. Patients were only considered healed when endoscopy after treatment revealed no ulcer.

Before treatment gastric acid secretion was determined in all patients with a duodenal ulcer and in 18 of the 24 gastric ulcer patients. After an overnight fast, a gastric tube was positioned according to the method described by Hector (12). Basal acid output was measured during one hour and subsequently maximal acid output during one hour after injection of pentagastrin (6 µg/kg i.m.). Hydrogen ion concentration (meq H^+/l) was determined by titration with 0.1N NaOH up to pH 7.0.

Gastric acid secretion after cimetidine was measured in 14 patients with a duodenal and in 8 patients with a gastric ulcer. In these patients gastric analysis was performed as described above one hour after oral intake of 200 mg cimetidine, with this difference that basal acid output was measured during 30 minutes.

For statistical analysis, Wilcoxon's rank sum test and X^2 test were used.

Results

The effect of cimetidine on gastric acid secretion

The basal as well as the pentagastrin stimulated gastric acid secretion decreased significantly in all patients after administration of cimetidine. In duodenal ulcer patients the basal acid output decreased by an average of 92% (range 79-100%; $p<0.01$) and the maximal acid output by an average of 58% (range 18-83%; $p<0.01$). In gastric ulcer patients basal acid output diminished by an average of 97% (range 92-100%; $p<0.05$) and maximal acid output by an average of 50% (range 27-94%; $p<0.01$) (fig 1).

The effect of cimetidine on ulcer healing and on ulcer symptoms

Patient characteristics are given in table 1. There were no significant differences between the cimetidine and the placebo groups regarding age, sex, duration of disease or gastric acid secretion.

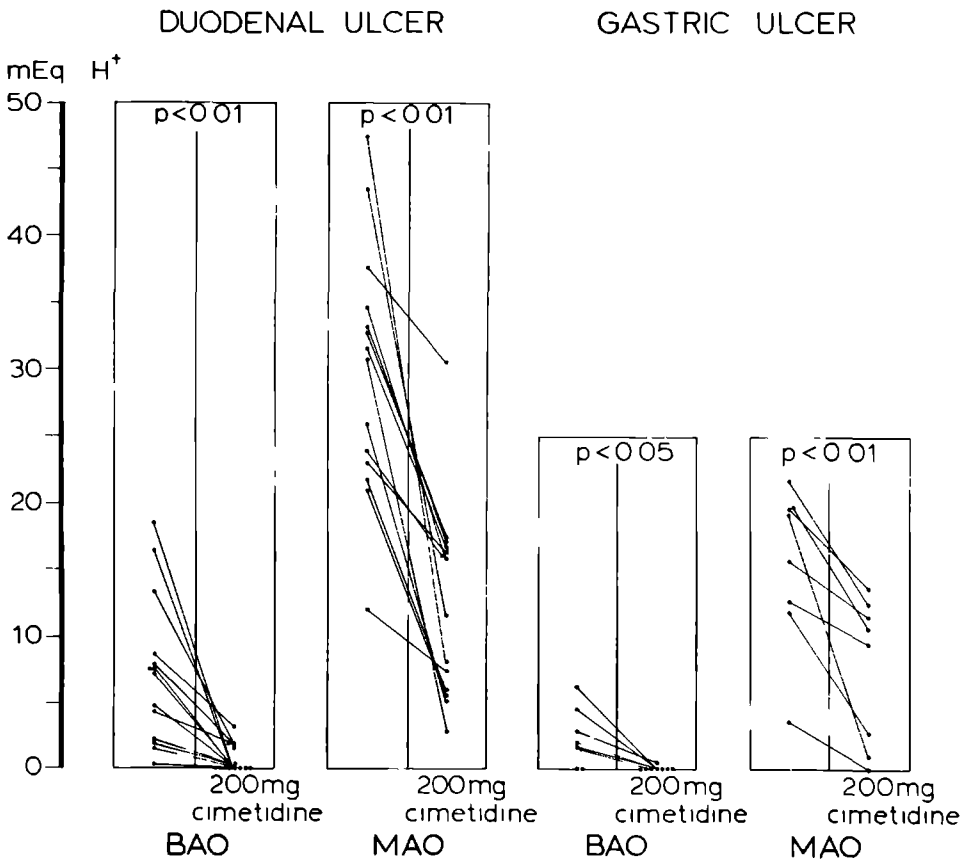

Fig 1 Basal (BAO) and maximal acid output (MAO) without medication and one hour after 200 mg cimetidine orally in 14 duodenal and 8 gastric ulcer patients. BAO was measured for 30 minutes and MAO was measured for one hour.

Duodenal ulcer

After 4 weeks treatment the ulcer had healed in 10 out of 12 patients treated with cimetidine and in 2 out of 11 patients on placebo ($p<0.01$) (table 2). Ulcer symptoms were expressed as the number of days with pain per week. The symptoms in the week prior to the trial were comparable in both groups. During treatment ulcer symptoms decreased in both groups of patients. However, only in cimetidine treated patients symptomatic improvement during treatment was statistically significant in all treatment weeks when compared to the week before the trial (fig 2).

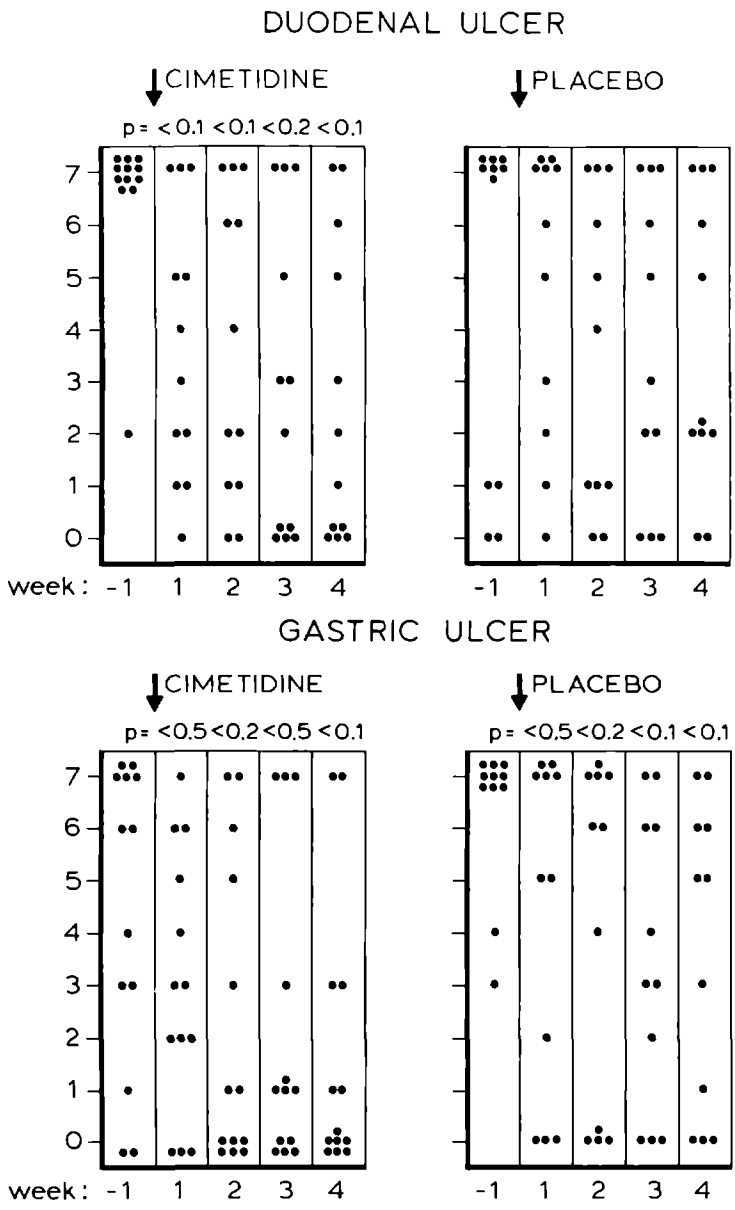

Fig 2 The effect of cimetidine and placebo on ulcer symptoms expressed as the number of days with ulcer symptoms weekly in the week prior to treatment (week -1) and during the 4 weeks of treatment (week 1-4), in duodenal (top panel) and gastric ulcer patients (bottom panel). Arrow indicates start of treatment. p-Values indicate statistical differences between treatment week compared with the one before the trial(week -1).

Table 1 CHARACTERISTICS OF PATIENTS

	Cimetidine	Placebo
Duodenal ulcer		
age (yr)	50 ± 4	49 ± 6
male/female	12 / 0	10 / 1
duration of disease (yr)	12 ± 2	7 ± 2
basal acid output (meq/hr)	8.3±1.6	4.2±0.9
maximal acid output (meq/hr)	29.6±3.0	24.3±2.0
Gastric ulcer		
age (yr)	49 ± 3	52 ± 3
male/female	11 / 2	5 / 6
duration of disease (yr)	3 ± 1	9 ± 3
basal acid output (meq/hr)	1.4±0.8*	1.8±0.3**
maximal acid output (meq/hr)	10.7±1.9*	13.0±1.9**

Data are presented as the mean ± SEM

* nine out of 13 patients studied

** nine out of 11 patients studied

Table 2 THE EFFECT OF CIMETIDINE AND PLACEBO ON ULCER HEALING

		healed	unhealed	
Duodenal ulcer	cimetidine	10	2	p<0.01
	placebo	2	9	
Gastric ulcer	cimetidine	9	4	ns
	placebo	4	7	

ns = the difference is statistically not significant

Gastric ulcer

After 4 weeks treatment the ulcers in 9 out of 13 cimetidine treated patients had healed compared with 4 out of 11 patients on placebo (ns) (table 2). In both cimetidine and placebo treated patients ulcer symptoms diminished significantly during treatment in all 4 weeks compared to the week prior to the trial (fig 2).

Side effects

One patient complained of headache and another of skin rash. Both had been as it turned out, on placebo. In 5 patients on cimetidine, who had shown normal serum creatinine concentrations (<100 µmol/l) before treatment, an increase to above-normal values was observed (102-115 µmol/l). These concentrations returned in all patients to initial values during further treatment with cimetidine, after the trial.

In 5 patients, who had increased serum creatinine concentrations (102-159 µmol/l) prior to cimetidine treatment, a further increase was observed (114-182 µmol/l), but also this increase was temporary as was shown during further treatment with cimetidine. In 2 patients receiving placebo a temporary increase in serum creatinine concentration to above-normal levels was observed (104 and 125 µmol/l).

During cimetidine treatment in 6 patients an increase in SGPT to above normal levels (16-45 u/l) was observed. In all 6 cases values were normal before treatment. The transaminase concentration normalized during further treatment with cimetidine. Two patients in the placebo group also had a temporary increase of SGPT levels (to 18 u/l).

The other laboratory tests studied continued to be normal.

Discussion

This study confirms that cimetidine greatly reduces gastric acid secretion. In duodenal, as well as gastric ulcer patients, basal and pentagastrin stimulated gastric acid secretion was greatly inhibited (13,14). Moreover, cimetidine proved to have a favourable effect on the healing of duodenal ulcer and had a clearly favourable effect on the ulcer symptoms of these patients. Our results are in agreement with those of other observers (7-11).

In gastric ulcer patients however, the effect of cimetidine treatment was less clear. Neither in the healing of ulcers, nor in the alleviation of ulcer symptoms, cimetidine proved to be superior over a placebo. A number of studies

report findings corresponding with our observation (15,16). Some investigators however, reported a significantly better effect of cimetidine compared to a placebo in the healing of gastric ulcers, but also in these studies no favourable effect of cimetidine treatment on ulcer symptoms could be established (17,18).

No important side effects were noted. Gynaecomastia, as reported by others (19,20), did not occur in any of our patients. In several patients, a slight transient rise of serum creatinine concentration and SGPT levels was observed. Comparing data of other investigators it would appear, that temporary serum creatinine increases occur in 11% of patients treated with cimetidine and in 6.6% of those receiving a placebo (21).

In conclusion: cimetidine was a potent inhibitor of gastric acid secretion. Furthermore, in duodenal ulcer patients cimetidine proved to be effective in healing ulcers and relieving ulcer symptoms. In gastric ulcer patients however, treatment with cimetidine was not superior over a placebo.

References

1 HOLLANDER D, HOSSAIN Z, SUFI AM: Inhibition of nocturnal acid secretion in duodenal ulcer patients by an H_2-histamine antagonist - Cimetidine. A controlled double blind investigation. Dig Dis 21: 361, 1976

2 LONGSTRETH GF, GO VLW, MALAGELADA J-R: Cimetidine suppression of nocturnal gastric secretion in active duodenal ulcer. N Engl J Med 294: 801, 1976

3 HENN RM, ISENBERG JI, VERNON MAXWELL BS et al: Inhibition of gastric acid secretion by cimetidine in patients with duodenal ulcer. N Engl J Med 293: 371, 1975

4 POUNDER RE, MILTON-THOMPSON GJ, WILLIAMS JG et al: 24-hour control of intragastric acidity by cimetidine in duodenal ulcer patients. Lancet II: 1069, 1975

5 RICHARDSON CT, WALSH JH, HICKS MI: The effect of cimetidine, a new histamine H_2-receptor antagonist, on meal stimulated acid secretion, serum gastrin, and gastric emptying in patients with duodenal ulcer. Gastroenterology 71: 19, 1976

6 POUNDER RE, WILLIAMS JG, RUSSELL GJ et al: Inhibition of food stimulated gastric acid secretion by cimetidine. Gut 17: 161, 1976

7 BLACKWOOD WS, MAUDGAL BP, PICKARD RG et al: Cimetidine in duodenal ulcer. Lancet 2: 174, 1976

8 BODEMAR G, WALAN A: Cimetidine in the treatment of active duodenal and prepyloric ulcers. Lancet 2: 161, 1976

9 BARDHAN KD, SAUL DM, BALMFORTH GV: The effect of cimetidine on duodenal ulceration. An interim report of a multicentre double-blind trial. In: Cimetidine: proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland, M Alison Simkins, Amsterdam. Excerpta Medica, 1977, p 260

10 GRAY GR, Mc KENZIE I, SMITH IS et al: Oral cimetidine in severe duodenal ulceration, a double blind controlled trial. Lancet 1: 4, 1977

11 SEMB LS, BERSTAD A, MYREN J et al: A double-blind multicentre comparative study of cimetidine and placebo in short-term treatment of active duodenal ulceration. In: Cimetidine: proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland, M Alison Simkins, Amsterdam. Excerpta Medica, 1977, p 248

12 HECTOR RM: Improved technique of gastric aspiration. Lancet 1: 15, 1968

13 AADLAND E, BERSTAD A, SEMB LS et al: Inhibition of pentagastrin-stimulated gastric secretion by cimetidine. In: Cimetidine: proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland, M Alison Simkins, Amsterdam. Excerpta Medica, 1977, p 87

14 BARBEZAT GO, BANK S: Basal acid output response to cimetidine in man. In: Cimetidine: proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland, M Alison Simkins, Amsterdam. Excerpta Medica, 1977, p 110

15 DYCK WP, BELSITO A, FLESHLER B et al: Cimetidine and placebo in the treatment of benign gastric ulcer. A multicenter double blind study. Gastroenterology 74: 410, 1978

16 CICLITIRA PJ, MACHELL RJ, FARTHING MJ et al: Double blind controlled trial of cimetidine in the healing of gastric ulcer. Gut 20: 730, 1979

17 BADER JP, MORIN T, BERNIER JJ et al: Treatment of gastric ulcer by cimetidine. A multicentre trial. In: Cimetidine: proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland, M Alison Simkins, Amsterdam. Excerpta Medica, 1977, p 287

18 FROST F, RAHBEK I, RUNE SJ et al: Cimetidine in patients with gastric ulcer: a multicenter controlled trial. Br Med J 2: 795, 1977

19 HALL WH: Breast changes in males on cimetidine. N Engl J Med 295: 841, 1976

20 BATESON MC, BROWNING MC, MACONNACHIE A: Galactorrhoea with cimetidine. Lancet II: 247, 1977

21 BURLAND WL, GLEADLE RI, MILLS JG et al: The effect of cimetidine on renal function. In: Cimetidine: proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland, M Alison Simkins, Amsterdam. Excerpta Medica, 1977, p 67

CHAPTER 3

CIMETIDINE IN ANASTOMOTIC ULCERATION AFTER PARTIAL GASTRECTOMY

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Abstract

In order to assess the efficacy of cimetidine in patients with endoscopically proved anastomotic ulcer after partial gastrectomy, 21 such patients entered a double blind prospective clinical trial. At endoscopy after 4 weeks of treatment, 8 of 12 patients treated with 1 g cimetidine daily compared with one of 9 patients who received a placebo had healed ulcers ($p<0.05$). Evaluation of symptom relief supported the efficacy of cimetidine compared with placebo. Healing rate after one month of treatment with cimetidine was 67% and increased to 86% after 2 months. During one year of maintenance therapy with 800 mg cimetidine daily, 3 of 19 patients relapsed. No serious side effects were observed. The results of this study demonstrate a beneficial effect of cimetidine on healing and symptoms of anastomotic ulcers.

Introduction

Partial gastrectomy is a widely used surgical treatment in patients with peptic ulcer disease. A number of these patients, however, suffer anastomotic ulceration. Recurrence rates differ, from 3.7% after subtotal gastrectomy alone to 0.7% if also vagotomy was performed (1).

Anastomotic ulcers differ from duodenal ulcer in that they occur usually with lower acid output. Furthermore, medical treatment of anastomotic ulcers is not as successful as that of duodenal ulcers, nor is surgical treatment, whereas the latter presents with a high mortality rate (2,3). It has been shown previously that H_2-receptor antagonists are beneficial in the treatment of duodenal ulcer (4,5,6). The present study was undertaken to assess the efficacy of the H_2-receptor antagonist cimetidine in the treatment of patients with anastomotic ulcer after partial gastrectomy.

Patients and methods

Twenty-one patients with anastomotic ulcer after partial gastrectomy with Billroth I (BI) or Billroth II (BII) anastomosis were studied. The ulcer was confirmed by endoscopy within 3 days of the patients' entering the trial. Only patients with ulcers measuring 5 mm in diameter (the diameter of an open biopsy forceps) or more were admitted to the trial.

Patients were treated as outpatients and were randomly, in double-blind fashion, allocated to cimetidine 3 times daily, 200 mg after meals and 400 mg at bedtime, or matching placebo. In addition, they were free to use antacid tablets, containing 578 mg calcium carbonate and 75.5 mg magnesium

carbonate per tablet, in case of ulcer dyspepsia. All other ulcer medication was discontinued. Patients who used drugs with known or suggested ulcerogenic properties were excluded from the study. A standard gastric analysis using pentagastrin, 6 μg/kg, was performed before the study in all but 4 patients. Each patient was given a diary card to record day and night ulcer symptoms and antacid consumption. Patients were seen at weekly intervals, and at each visit they were asked for symptoms and side effects and diary cards were checked. Before, after 2 weeks, and at the end of the trial, routine hematologic and biochemical blood studies and urine analysis were performed (hemoglobin, hematocrit, red blood cell count, total white blood cell count, differential and platelet count, creatinine, urea, uric acid, bilirubin, alkaline phosphatase, SGOT and SGPT). After 4 weeks of treatment, endoscopy was repeated, and ulcers were recorded as either healed or unhealed. For statistical analysis, Wilcoxon's rank sum test and χ^2 test were used.

Results

Patient characteristics are given in table 1.

Table 1 PATIENT CHARACTERISTICS AND HEALING RATE

	Cimetidine	Placebo
age (yr)	48 ± 4	42 ± 4
male/female	12 / 0	8 / 1
duration of disease (yr)	14 ± 3	15 ± 3
Billroth I/Billroth II anastomosis	3 / 9	1 / 8
year after operation	9 ± 2	8 ± 2
duration of present relapse (wk)	45 ± 17	39 ± 11
basal acid output (meq/hr)	2.3 ± 1.0*	2.1 ± 0.4**
peak acid output (meq/hr)	14.0 ± 4.1*	11.0 ± 2.4**
serum gastrin (pg/ml)	48 ± 5	50 ± 10
healed/not healed	8 / 4	1 / 8

Data are presented as the mean ± SEM

* nine of 12 patients studied; ** eight of 9 patients studied

Only 3 patients, 2 in the placebo group and one treated with cimetidine, had also undergone vagotomy. There were no significant differences between the groups for age, sex, duration of disease or current relapse, incidence of BI or BII anastomosis, fasting serum gastrin levels, or gastric acid secretion. All patients had fasting serum gastrin levels within the normal range at the time of entrance in the trial (normal <115 pg/ml). Nevertheless, one patient (the only female) subsequently had slightly elevated serum gastrin levels (160 pg/ml), with marked increases after administration of calcium and secretin suggestive of the Zollinger-Ellison syndrome (7). Her ulcer did not heal on placebo. After 4 weeks of treatment, ulcers in 8 of 12 cimetidine-treated patients were healed, compared with one of 9 patients receiving placebo ($p < 0.05$). Analysis of duration of disease, current relapse, or gastric acid secretion revealed no difference between patients whose ulcers were healed and patients whose ulcers did not heal. Data for ulcer symptoms are shown in figure 1. Symptoms were analyzed as days and nights with ulcer pain. The symptoms in the week before the trial were not significantly different between the 2 groups of patients. Both cimetidine- and placebo-treated patients experienced marked relief of ulcer symptoms during the trial. There was a significant improvement of day symptoms in the 2nd, 3rd, and 4th treatment week compared with day symptoms in the week before the trial in the cimetidine-treated patients ($p < 0.05$, $p < 0.02$, $p < 0.02$) which was achieved only in week 4 in placebo-treated patients ($p < 0.05$). The improvement in night symptoms was significant in all 4 treatment weeks compared with the symptoms in the week preceding the trial in cimetidine-treated patients ($p < 0.02$, $p < 0.02$, $p < 0.01$, $p < 0.01$) and in week 1, 2 and 3 of placebo treated patients ($p < 0.05$, $p < 0.01$, $p < 0.02$). Cimetidine-treated patients experienced significantly more pain-free nights in the 3rd and 4th treatment week than those who were on placebo ($p < 0.02$). There was no difference in ulcer symptoms between patients whose ulcers healed and patients whose ulcers did not heal after 4 weeks in each treatment group. Data for antacid consumption are given in table 2.

Table 2 ANTACID CONSUMPTION

	week 1	week 2	week 3	week 4
	(tablets per week, mean ± SEM)			
Cimetidine	8 ± 4	5 ± 3	5 ± 3	5 ± 3
Placebo	19 ± 8	21 ± 9	19 ± 6	17 ± 5

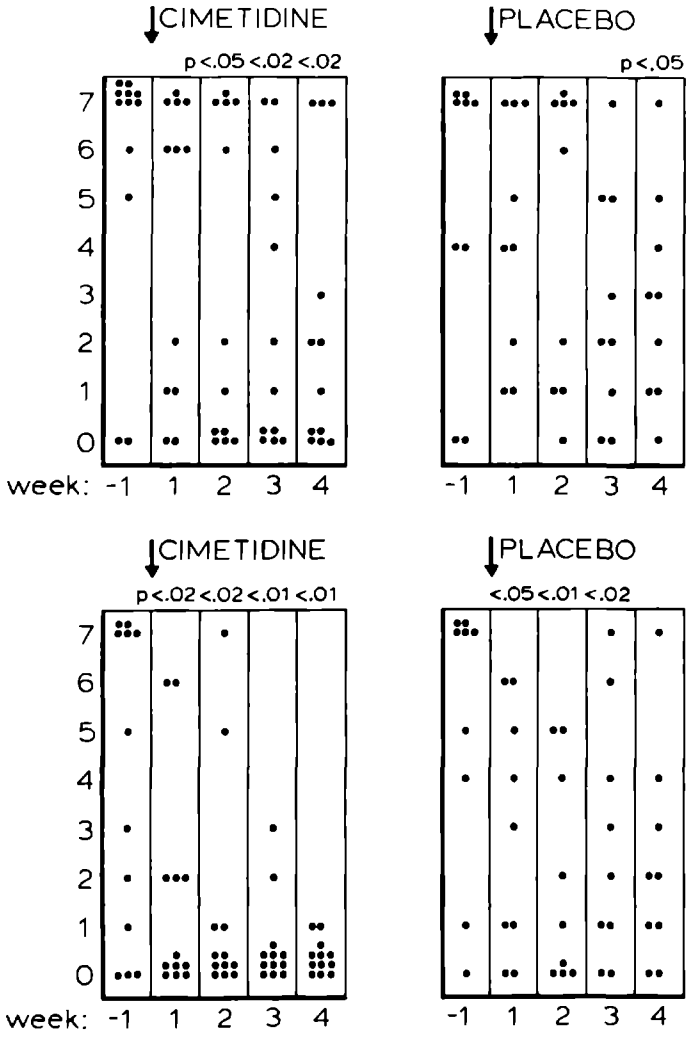

Fig 1 The effect of cimetidine and placebo on ulcer symptoms expressed as days (top panel) and nights (bottom panel) with ulcer symptoms a week, in the week prior to the trial (week -1) and the 4 weeks of the trial (week 1-4). Arrow indicates start of treatment. p-Values indicate statistical difference of concerning treatment week compared with the week prior to the trial (week -1).

Cimetidine-treated patients consumed fewer antacids than those on placebo, but none of the differences was statistically significant. During the trial, no side effects were reported. Only slight transient elevation of serum creatinine levels was seen in 2 patients on cimetidine and one on placebo; in 2 cimetidine-treated patients, a transient rise above normal SGPT was seen. No other changes in blood and urine were observed.

After completion of the trial, all patients whose ulcers were not healed were treated with an additional course of 1 g cimetidine daily. After 4 weeks, 3 of the 4 cimetidine failures and 5 of the 8 patients whose ulcers did not heal on placebo had healed ulcers. In the remaining 4 patients, ulcers healed after 2, 4, 5, and 10 months of treatment with cimetidine, respectively; all were symptom free long before their ulcers healed. No relation between acid output and ulcer healing was found. All patients whose ulcers healed entered an open maintenance treatment study with 400 mg cimetidine after breakfast and at bedtime. Two patients were lost to follow-up. Up to this time, of the 19 patients treated for one year or longer, 3 have had a relapse, clinically confirmed by endoscopy. Of the 16 patients who did not relapse, 12 underwent repeat endoscopy after one year of treatment and were found to have no ulcer.

Discussion

This study shows, as our preliminary data already suggested (6), that cimetidine promotes healing and alleviates symptoms of anastomotic ulcers after partial gastrectomy. Only one double-blind study on the effect of cimetidine in patients with recurrent ulcer after gastric surgery has previously been reported (8). That study did not show a better healing of such ulcers by cimetidine compared with placebo, but only 3 antrectomized patients were in the heterogeneous group of subjects studied.The proportion of healed ulcers with cimetidine in our study (67%) is lower than that in most duodenal ulcer trials (>80%). Similarly, the proportion of ulcers healed on placebo (11%) is lower than that reported in duodenal ulcer (25-60%) (4-6). This demonstrates the lower tendency of anastomotic ulcers to heal spontaneously. After 4 and 8 weeks of cimetidine treatment, the ulcers in 67% and 86% of the patients, respectively, had healed. This suggests that a longer treatment course may be indicated in this condition. In 3 patients with long histories (13-41 year) and with large ulcers who were totally symptom free during cimetidine treatment, we saw the ulcers gradually decrease while it took months before they were healed. From this study, we cannot conclude whether

prolonging treatment is more effective than increasing the dose of cimetidine in patients with delayed ulcer healing.

Results of maintenance treatment in the present study are promising, although the numbers of patients were relatively small and the study was not double blind. Relapse rate was only 16% in one year, even though this type of ulcer is notorious for a high tendency to relapse (3). This study of long-term cimetidine treatment, however, does not allow us to draw conclusions about the need for or the best type of long-term treatment in patients with anastomotic ulcers after partial gastrectomy.

Now that the efficacy of cimetidine has been shown in these patients, studies comparing cimetidine with other treatment regimens, either medical or surgical, are indicated.

References

1 POSTLETHWAIT RW: Five year follow-up result of operations for duodenal ulcer. Surg Gynaecol Obstet 137: 387, 1973

2 BARON JH: The clinical use of gastric function tests. Scand J Gastroenterol 5 (suppl 6): 9, 1970

3 STABILE BE, PASSARO E: Recurrent peptic ulcer. Gastroenterology 70:124,1976

4 BODEMAR G, NORLANDER B, WALAN A: Cimetidine in the treatment of active peptic ulcer disease. In: Cimetidine: Proceedings of the Second International Symposium on Histamine H_2-receptor Antagonists. Edited by WL Burland MA Simkins, Amsterdam-Oxford, Excerpta Medica, 1977 p 224

5 BINDER HJ, COCCO A, CROSSLEY RJ et al: Cimetidine in the treatment of duodenal ulcer: a multicenter double-blind study. Gastroenterology 74: 380, 1978

6 FESTEN HPM, LAMERS CBH, VAN TONGEREN JHM: De onderdrukking van de maagzuurproductie door middel van cimetidine, resultaten van een dubbelblind onderzoek naar de betekenis van cimetidine voor de behandeling van peptische ulcera. Ned T Geneesk 122: 862, 1978

7 LAMERS CBH, VAN TONGEREN JHM: A comparative study of the value of the calcium, secretin and meal stimulated increase in serum gastrin to the diagnosis of the Zollinger-Ellison syndrome. Gut 18: 128, 1977

8 KENNEDY T, SPENCER A: Cimetidine for recurrent ulcer after vagotomy or gastrectomy: a randomised controlled trial. Br Med J 1: 1242, 1978

CHAPTER 4

CIMETIDINE IN THE TREATMENT OF SEVERE ULCERATIVE REFLUX OESOPHAGITIS; RESULTS OF AN 8 WEEKS DOUBLE BLIND STUDY AND OF SUBSEQUENT LONG TERM MAINTENANCE TREATMENT

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Abstract

Twenty patients with endoscopic evidence of severe ulcerative reflux oesophagitis were treated with cimetidine, 1.6 g daily, or placebo, in a double blind controlled trial. After 8 weeks 6 out of 13 cimetidine treated patients were healed and one out of 7 patients on a placebo ($p = 0.18$). During the treatment symptom relief was not significantly different in cimetidine in comparison to placebo treated patients. In those patients healed on cimetidine during the trial however, symptomatic response was significantly better compared to the unhealed patients on cimetidine and those on placebo.Gastric acid output did not differentiate between responding and non-responding patients. Healing rate with cimetidine was not improved by prolonged treatment. During one year maintenance treatment with 400 mg cimetidine twice daily 6 out of 7 patients suffered relapse oesophagitis.

It has been concluded that short term cimetidine treatment of severe ulcerative reflux oesophagitis was beneficial in approximately 50% of the patients only. Since this severe oesophagitis tends to relapse in spite of low dose cimetidine maintenance therapy, the main advantage of this treatment is preparation for more definite measures, e.g. surgery.

Introduction

Cimetidine is an effective inhibitor of gastric acid secretion. Gastric acid is supposed to play an important role in the pathogenesis and the symptomatology of reflux oesophagitis (1,2). Therefore we studied the effect of treatment with cimetidine on healing and symptoms of reflux oesophagitis in a controlled double blind study. As reflux oesophagitis after cessation of medical treatment tends to relapse (3), we subsequently studied the effect of open maintenance treatment with cimetidine in all healed patients.

Patients and methods

Twenty-three patients with evidence of severe ulcerative reflux oesophagitis at endoscopy immediately prior to entrance in the trial were studied. In none of the patients and oesophageal stricture was present. The patients were treated as out-patients and were randomly allocated to cimetidine, 400 mg after meals and at bedtime, or matching placebo during 8 weeks. They were free to use Gaviscon ^{R} tablets (260 mg alginic acid, 260 mg sod. alginate, 260 mg magn. trisilic., 104 mg alum. hydr. colloid, 88.5 mg sod. bicarbonate per tablet) in case of heartburn symptoms. No other drugs were prescribed and

no other measures were taken during the trial. In 17 patients a standard gastric analysis before and after 6 µg/kg pentagastrin i.m. was performed before the study. Diary cards were used by each patient to record day and night heartburn symptoms and the number of Gaviscon ^{R} tablets used. Patients were seen at bi-weekly intervals and at each visit they were asked for symptoms and side effects, diary cards were checked and routine haematological and biochemical blood studies and urinalysis were performed (haemoglobin, haematocrit, red blood cell count, total white blood cell count, differential and platelet count, creatinine,urea, uric acid, bilirubin, alkaline phosphatase, SGOT and SGPT).

Data about symptoms before treatment were obtained from the patients history. Symptomatic effect of treatment during the trial was analysed as days and nights without heartburn from the diary cards. After 8 weeks of treatment endoscopy was repeated and oesophagitis was recorded as healed or unhealed. Oesophagitis was considered healed only if at endoscopy no mucosal lesions were seen.

All patients with unhealed oesophagitis were treated with additional open courses with cimetidine 1.6 g daily and endoscopy was repeated every 8 weeks. If no healing occurred after 16 weeks treatment with cimetidine, the treatment was judged as a failure.

Patients with healed oesophagitis entered open long term maintenance treatment with cimetidine 400 mg after breakfast and at bedtime. Endoscopy was repeated in case of recurrent symptoms or after one year treatment in patients who remained free of symptoms.

For statistical analysis Student's t-test and Fisher's exact test were used.

Results are expressed as mean $\pm$ 1 SEM.

Results

Three patients were withdrawn from the final analysis because of lack of cooperation, refusal of repeat endoscopy and co-existent oesophageal carcinoma. Characteristics of the remaining 20 patients are given in table 1. Thirteen patients were treated with cimetidine and 7 with placebo. There was no statistically significant difference between the 2 treatment groups regarding age, duration of disease and gastric acid secretion. Seven patients in the cimetidine group were female compared to one treated with placebo.

After 8 weeks 6 out of 13 cimetidine treated patients compared to one out

of 7 on placebo were healed (p = 0.18; ns). Three out of the 6 with cimetidine healed patients were female (ns).

Table 1. PATIENT CHARACTERISTICS, HEALING RATE AND PRE-TRIAL SYMPTOMS.

	Cimetidine (n = 13)	Placebo (n = 7)
age (yr)	60 ± 5	46 ± 6
male/female	6 / 7	6 / 1
duration of disease (yr)	6 ± 2	8 ± 3
basal acid output (mmol H^+/h)	0.7 ± 0.4*	2.1 ± 1.3**
maximum acid output (mmol H^+/h)	8.9 ± 2.5*	11.2 ± 3.1**
healed (male/female)	6 (3/3)	1 (1/0)
pre-trial symptoms:		
-days per week with pain	4.7 ± 1	5.2 ± 1.2
-nights per week with pain	3.7 ± 1	5.0 ± 1.2

Data are presented as the mean ± SEM

* ten out of 13 patients studied; ** six out of 7 patients studied

Symptoms before treatment were not different in both treatment groups (table 1). During the trial one patient in the cimetidine group and one on placebo did not record their symptoms properly and they were excluded from the symptom-analysis. In the remaining 18 patients there was no difference between the cimetidine and the placebo treated groups, neither for days nor for nights without symptoms (figure 1).

Only 4 patients in the cimetidine group and 4 in the placebo group used Gaviscon^R tablets during the trial. As in these patients the mean number of tablets consumed per day was less than one, these data were not analysed.

The patients in the cimetidine group were divided in 2 sub-groups: those who healed and those who did not heal during the trial. If the symptoms of these 2 sub-groups and of placebo treated patients were analysed a deviating picture was seen. The number of symptomfree days and nights in patients healed on cimetidine during the trial was significantly higher in all treatment weeks ($p < 0.05$ to $p < 0.001$) in comparison to patients unhealed by

cimetidine. Compared to patients on placebo patients healed with cimetidine experienced significantly more painfree days in week 5,6,7 and 8 of treatment ($p < 0.05$) and more painfree nights in week 6 and 8 ($p < 0.05$). During the whole trial period no significant differences were observed between the symptoms of the cimetidine resistent patients and the symptoms of the placebo group (figure 2).

In the week prior to the trial the number of days with heartburn symptoms in the patients healed on cimetidine was 3.5 ± 1.6 and in those unhealed 5.0 ± 1.3; the number of nights with symptoms was 2.3 ± 1.5 and 4.3 ± 1.2 respectively. Collation of pre-trial symptoms in the cimetidine healed and unhealed group, and in the placebo group revealed no statistical differences. Gastric acid secretion of patients healed by cimetidine (BAO 1.0 ± 0.6 mmol H^+/h; MAO 7.6 ± 2.8 mmol H^+/h; n = 6) was not different from those not healed on cimetidine (BAO 0.3 ± 0.1 mmol H^+/h; MAO 10.8 ± 5.0 mmol H^+/h; n = 4).

After the trial all unhealed patients were treated with subsequent open courses of cimetidine. After 8 weeks one patient from the cimetidine group and 2 from the placebo group showed healed oesophagitis. After 16 weeks one additional patient of the placebo group achieved remission. In total 10 patients healed during cimetidine treatment, one healed on placebo and 9 patients did not respond to treatment. Gastric acid secretion of non-responding patients (BAO 1.5 ± 1.3 mmol H^+/h; MAO 10.4 ± 4.0 mmol H^+/h; n = 6) was not different from patients responding to cimetidine therapy (BAO 1.1 ± 0.4 mmol H^+/h; MAO 9.3 ± 2.1 mmol H^+/h; n = 10).

All 11 healed patients entered open maintenance treatment with 400 mg cimetidine after breakfast and at bedtime. Four patients were lost to follow-up. Of the remaining 7 patients 6 suffered endoscopically proven relapse oesophagitis during one year treatment. All relapses except one were symptomatic. The patient who did not relapse during this year was previously healed by placebo.

No side effects were reported during the trial and during maintenance treatment. Only slight transient elevations of serum creatinine levels were seen in 3 cimetidine and 2 placebo treated patients. No other changes in blood and urine parameters were observed.

Discussion

Various investigators reported different results of treatment with

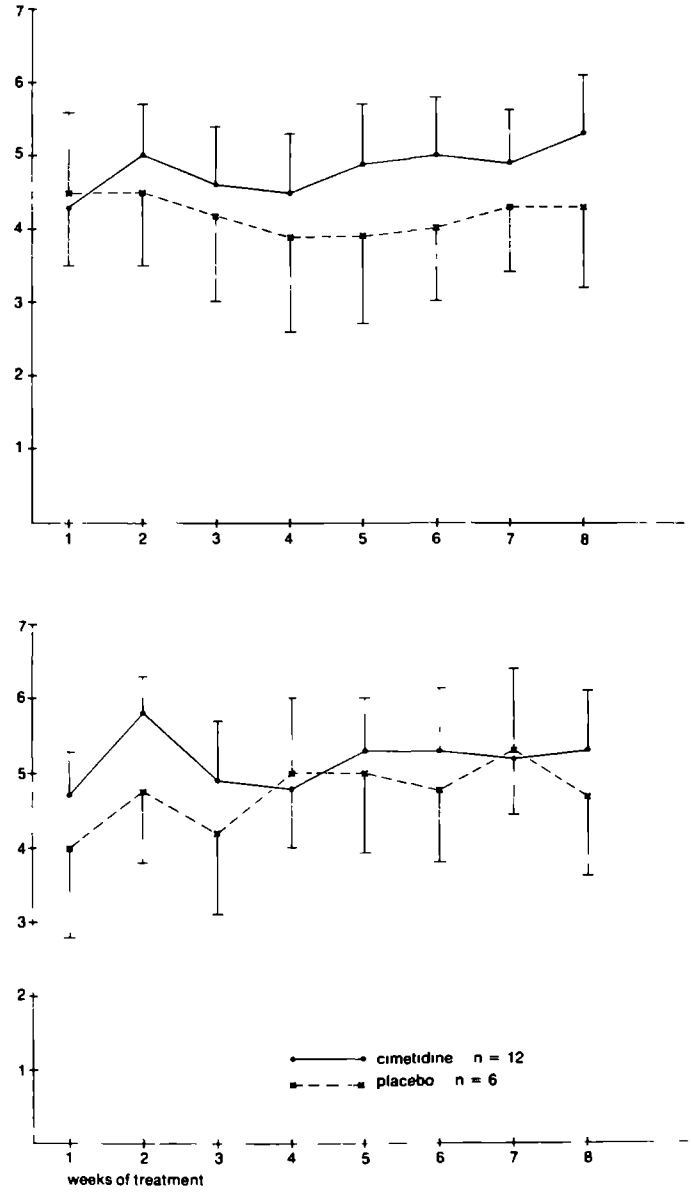

Fig 1 The effect of treatment with cimetidine (solid line) and placebo (broken line) on heartburn symptoms, expressed as painfree days (upper panel) and nights (lower panel) a week, during the 8 weeks of the trial. Data are presented as the mean ± SEM.

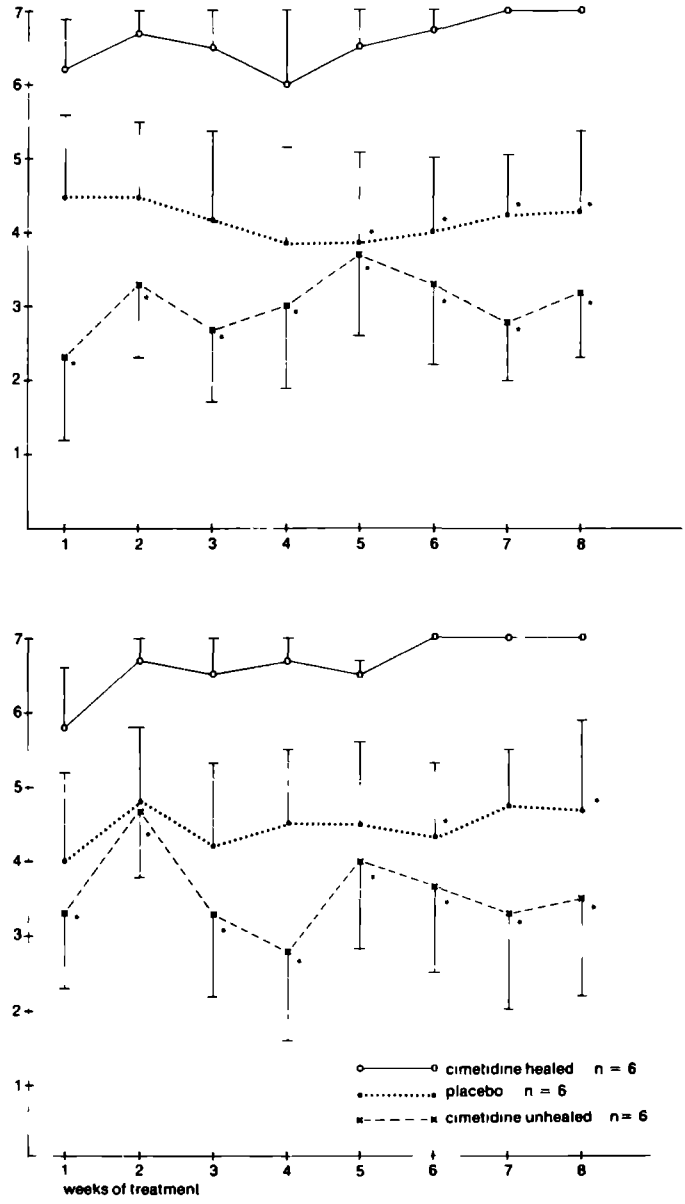

Fig 2 The effect of trial treatment on heartburn symptoms expressed as pain-free days (upper panel) and nights (lower panel) a week in patients healed with cimetidine (solid line), in patients not healed with cimetidine (broken line) and placebo treated patients (dotted line) during the 8 weeks of the trial. Data are presented as the mean ± SEM. Asterisks indicate data significantly different from patients healed on cimetidine ($p<0.05$).

cimetidine in gastro-oesophageal reflux disease (3-6). Most studies showed a significant effect of cimetidine on symptoms compared to a placebo while no significantly better healing of oesophagitis occurred (3,4,5). In only some of these studies improved healing as well as substantial symptom relief by cimetidine was reported (4,6). In all these studies patients with different grades of oesophagitis were included. There is only one report of cimetidine treatment in which solely patients with severe ulcerative oesophagitis were included. In this study oesophagitis improved significantly whereas symptoms did not. In these patients, however, an oesophageal stricture was present which might have influenced the results (7). In our study cimetidine was not superior to a placebo in the healing and alleviation of symptoms of severe ulcerative reflux oesophagitis. This absence of significance in healing could be attributed to the single patient who healed on placebo. This was also the only patient who did not relapse during maintenance treatment. Thus behaviour of oesophagitis in this patient seems to be different from other patients.

Healing rate with cimetidine was about 50% and healing correlated well with symptomatic relief. Patients who responded well to the drug had rapid symptom relief whereas in others who did not respond symptom relief was absent. Prolonging treatment, as suggested by others (4) did not improve the effect of cimetidine.

We have not been able to define criteria to differentiate between the responders and non-responders to cimetidine. Gastric acid output certainly was not useful, as this was not different between healed and unhealed patients. Apparently, gastric acid does not always play a key role in this condition and other factors are of varying aetiological importance. It may be assumed that gastric acid secretion was sufficiently inhibited by the dose of cimetidine used in these patients. It is therefore not likely that an increase of the dose will improve the chance of healing.

This report presents also data on the effect of maintenance treatment with low dose cimetidine to prevent recurrent oesophagitis. Although the number of patients was small and treatment was not double-blind the outcome was clear: cimetidine in a dose of 800 mg daily does not prevent relapse of severe ulcerative reflux oesophagitis. From this study we cannot conclude whether a higher maintenance dose is suitable to prevent relapses.

In conclusion cimetidine was not superior to a placebo in the short term treatment of severe ulcerative reflux oesophagitis. Yet some patients respond

well to cimetidine therapy. Since symptomatic relief in these patients is rapid, an attempt with cimetidine seems indicated in patients resistant to other forms of medical therapy. However, since this severe form of oesophagitis tends to relapse and recurrence is not prevented by low dose cimetidine, subsequent surgical treatment, if feasible, will usually be indicated.

References

1 BERNSTEIN LM, BAKER LA: A clinical test for oesophagitis. Gastroenterology 34: 760, 1958

2 ISMAIL BEIGI F, HORTON PF, POPE II CE: Histologic consequences of gastro-oesophageal reflux in man. Gastroenterology 58: 163, 1970

3 BEHAR J, BRAND D, BROWN FC et al: Cimetidine in the treatment of symptomatic gastrooesophageal reflux. Gastroenterology 74: 441, 1978

4 LEPSIEN G, SONNENBERG A, BERGES W et al: Die Behandlung der Refluxösophagitis mit Cimetidin. Dtsch Med Wschr 104: 901, 1979

5 POWELL-JACKSON PR, BARKLEY H, NORTHFIELD TC: Effect of cimetidine in symptomatic gastro-oesophageal reflux. Lancet II: 1068, 1978

6 WESDORP E, BARTELSMAN J, DEKKER W et al: Oral cimetidine in reflux oesophagitis: a double blind controlled trial. Gastroenterology 74: 821, 1978

7 FERGUSON R, DRONFIELD MW, ATKINSON M: Cimetidine in treatment of reflux oesophagitis with peptic stricture. Brit Med J 2: 472, 1979

LONG-TERM TREATMENT WITH HISTAMINE H_2-RECEPTOR ANTAGONISTS IN ZOLLINGER-ELLISON SYNDROME

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Abstract

Continuous treatment of 3 Zollinger-Ellison patients with histamine H_2-receptor antagonists for 14, 26 and 31 months resulted in effective relief of complaints and marked reduction in gastric acid secretion. In one of the patients the dose of cimetidine had to be doubled after 15 months of treatment because of a rise in basal gastric acid secretion accompanied by recurrent diarrhea. Fasting and secretin stimulated serum gastrin levels were not affected by long-term treatment with histamine H_2-receptor antagonists. No side-effects were observed in the 3 patients on long term treatment.

Introduction

Histamine H_2-receptor antagonists have proved to be potent inhibitors of pentagastrin stimulated gastric acid secretion (1). These drugs have therefore been used in the treatment of hypersecretion of gastric acid in patients with the Zollinger-Ellison syndrome (2-8).

Reports on long term efficacy of H_2-receptor antagonists, however, are conflicting (9,10). Bonfils et al (9) found partial reduction in efficacy in one and total inefficacy in 5 out of 10 cases with Zollinger-Ellison syndrome treated for 15-190 days. McCarthy et al (10) on the other hand, found histamine H_2-receptor blocking agents effective in all 7 Zollinger-Ellison patients treated for one to 15 months.

In this study we report on the effect of long term treatment with histamine H_2-receptor antagonists on basal gastric acid secretion, fasting and secretin stimulated serum gastrin concentrations and clinical symptoms in 3 Zollinger-Ellison patients during continuous treatment for 14, 26 and 31 months.

Patients and methods

In all 3 patients the diagnosis of Zollinger-Ellison syndrome was based upon basal gastric hypersecretion (12-67 mmol/hr), fasting hypergastrinaemia (340-595 pg/ml), serum gastrin responses of at least 50% of basal value both to calcium, 15 mg/kg/3 hr and to secretin GIH (GIH Laboratories, Karolinska Institutet, Stockholm, Sweden), 1 CU/kg/30 sec and postprandial increases in serum gastrin of less than 50% of basal level (fig 1 and table 1). All 3 patients originated from families with multiple endocrine adenomatosis type I.

Table 1 EFFECT OF LONG TERM TREATMENT WITH HISTAMINE H_2-RECEPTOR ANTAGONISTS ON FASTING AND SECRETIN-STIMULATED SERUM GASTRIN LEVELS IN 3 PATIENTS WITH ZOLLINGER-ELLISON SYNDROME

Case	Date	Treatment	serum gastrin (pg/ml)			
			0	+5 min	+10 min	+15 min
1	1/6/75	-	595	1,300	990	760
	8/27/75	metiamide 400 mg	810	1,680	1,450	1,150
	11/19/76	cimetidine 400 mg	755	1,450	1,015	875
	6/27/77	cimetidine 400 mg	820	1,630	1,310	890
2	8/12/75	-	340	910	715	530
	9/9/75	metiamide 200 mg	340	1,440	990	740
	5/11/77	cimetidine 400 mg	330	1,450	1,040	770
3	7/25/75	-	440	990	820	630
	5/13/77	cimetidine 400 mg	330	1,010	890	590

Secretin (GIH-laboratories, Karolinska Institutet, Stockholm, Sweden) in a dose of 1 CU /kg/30 sec, was administered intravenously at time 0, corresponding to 2 hours after the oral intake of the drug.

Case report

Case 1: a 40-year old man had suffered from diarrhea and weight loss since 1965. In 1974 a diagnosis of Zollinger-Ellison syndrome and presumptive hyperparathyroidism was made. From January,1974 to March,1975 the patient was treated with high doses of anticholinergic drugs resulting in only moderate relief of diarrhea. In March,1975 a treatment with metiamide was started.

Case 2: a 39-year old woman had 3 pancreatic β-islet cell tumors resected in 1954. In 1968 3 hyperplastic parathyroid glands were resected for hyperparathyroidism. Since 1967 she had suffered from recurrent duodenal ulcers and diarrhea. In 1975 a diagnosis of Zollinger-Ellison syndrome was made. Treatment with metiamide was started in August,1975. At that time the patient had diarrhea but no active duodenal ulcer.

Case 3: a 38-year old woman had suffered from gastric pain, heartburn, diarrhea and weight loss since 1972. In 1975 a diagnosis of Zollinger-Ellison syndrome and presumptive hyperparathyroidism was made. From March,1976 to

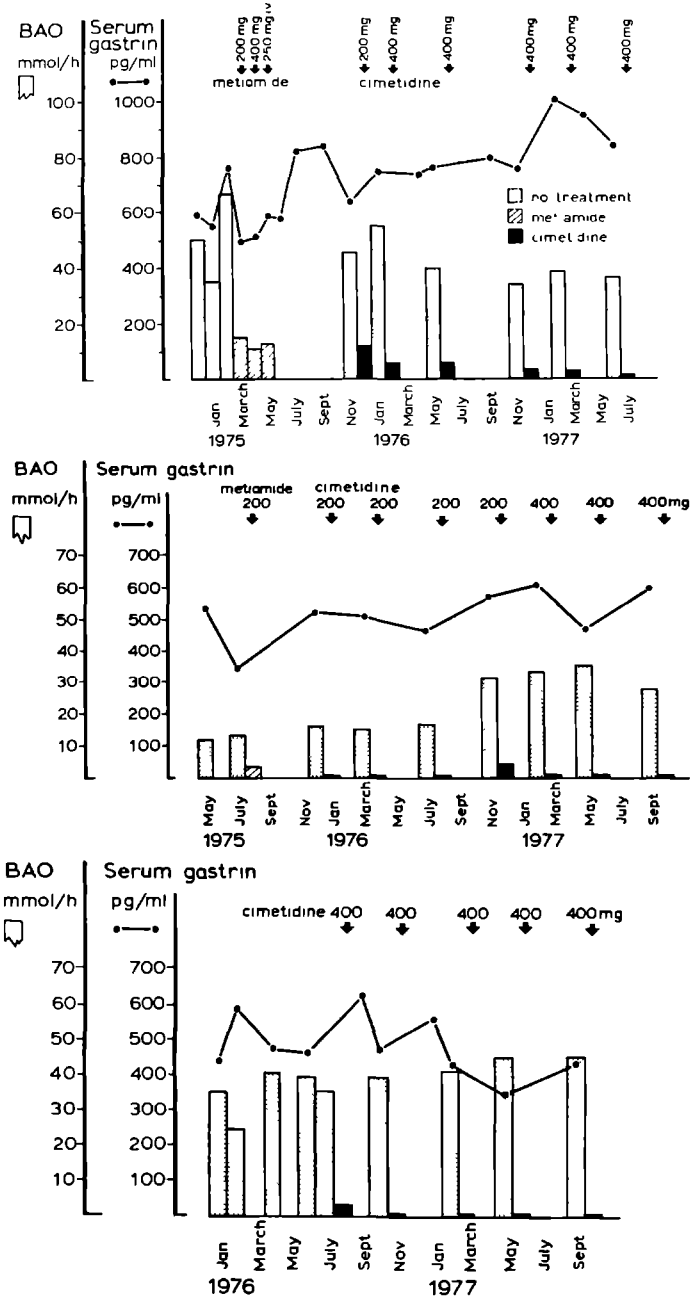

Fig 1 The effect of long term treatment with histamine H_2-receptor antagonists on basal gastric acid secretion and serum gastrin in 3 patients with Zollinger-Ellison syndrome. The upper diagram represents case 1, the middle case 2 and the lower case 3.

August, 1976 she was treated with high doses of anticholinergic drugs resulting in only moderate relief of complaints. In August 1976 treatment with cimetidine was started. At that time the patient had severe diarrhea and an active postbulbar ulcer.

Gastric aspiration was performed as described by Hector (11). Gastric acid was determined by titration of gastric juice with 0.1 N NaOH up to pH 7.0. The basal gastric acid output was measured after discontinuing the drug for 36 hours and also between one and 2 hours after the oral intake of the histamine H_2-receptor antagonist. In case 1 the basal gastric acid secretion was also measured during intravenous infusion of metiamide (fig 1).

Serum gastrin concentrations were measured by radioimmunoassay (12). Venous blood was drawn after an overnight fast, immediately before gastric intubation or the ingestion of the drug. Serum gastrin levels using this assay were 66 ± 18 (SD) pg/ml in 100 normal controls and 70 ± 20 pg/ml in 80 duodenal ulcer patients. Blood, liver and kidney toxicity tests were done biweekly in metiamide and every 4 weeks in cimetidine treated patients.

Results

Case 1 was treated with 1.0 g of metiamide daily, 0.2 g after meals and 0.4 g at bedtime from March,1975. In May,1975 the dose was increased to 2.0 g daily, 0.4 g after meals, at bedtime and at midnight, because of a poor clinical response. This latter dose led to a marked relief of diarrhea, a decrease in fecal fat excretion from 32-15 g daily and a weight gain of 4 kg within 5 months. From October, 1975 he suffered from recurrent attacks of abdominal pain with raised levels of amylase in blood and urine and a diagnosis of pancreatitis and gallstones was made.In November,1975 metiamide was replaced by cimetidine in the same dosage. In February,1976 liver tests showed partial biliary tract obstruction and at laparotomy an expanded gallbladder containing multiple small gallstones and an enlarged, nodular and firm pancreas were found. Choledochoduodenostomy and cholecystectomy were performed. A biopsy from the pancreatic body confirmed the diagnosis of pancreatitis but failed to reveal tumor lesions. About 3 months after surgery the patient developed overt pancreatic insufficiency and diabetes mellitus. Replacement therapy with pancreatic extract and insulin was started. At present, the patient is in a reasonable general condition without pain but with moderate diarrhea and steatorrhea of about 15 g daily. The basal gastric acid output, both without and with histamine H_2-receptor antagonists and the

fasting serum gastrin levels are shown in figure 1.

Case 2 was treated from August,1975 to November,1975 with 0.8 g of metiamide daily, 0.2 g after meals and at bedtime. From November,1975 to November, 1976 she received 0.8 g of cimetidine daily, resulting in complete disappearance of diarrhea, a decrease in fecal fat excretion from 12-6 g daily and a weight gain of 2 kg. In November,1976 she experienced recurrence of diarrhea. Basal gastric acid output, both without and with cimetidine, was found to be higher than previously (fig 1). For that reason the dose of cimetidine was increased up to 1.6 g daily, 0.4 g after meals and at bedtime, resulting in a complete disappearance of diarrhea.

Case 3 was treated from August,1976 with 1.0 g of cimetidine daily, 0.4 g after breakfast and 0.2 g after lunch, after dinner and at bedtime. This treatment resulted in marked relief of complaints, healing of the postbulbar ulcer after 6 weeks, a decrease in fecal fat excretion from 17-7 g daily and a weight gain of 7 kg within 10 months. Results of basal acid secretion, with and without histamine H_2-receptor antagonists and fasting serum gastrin levels are shown in figure 1.

The results of the gastrin responses to secretin GIH 1 CU/kg/30 sec, before and during treatment with H_2-receptor antagonists are presented in table 1.

Repeated laboratory tests did not show any hematological, renal or liver toxicity. None of the patients had gynecomastia, galactorrhea or elevated serum prolactin levels (less than 14 ng/ml; normal value less than 20 ng/ml). Detailed study of the cellular and humoral immunology (mixed lymphocyte culture, skin tests, autoantibody production and serum immunoglobulin concentration) in cases 1 and 2 after treatment with histamine H_2-receptor antagonists for 25 and 20 months respectively, revealed no abnormalities (13).

Comment

This study shows that histamine H_2-receptor antagonists are able to inhibit gastric acid secretion in Zollinger-Ellison patients for periods up to two and a half years. In one patient (case 2) the dose of cimetidine had to be increased in order to maintain adequate inhibition of gastric acid secretion. This was not attributable to a reduction in efficacy but was found to be related to a rise in basal gastric acid output. Since fasting serum gastrin levels did not greatly change in this patient, an increased sensitivity of the parietal cells to gastrin might have been involved in the rise in gastric acid secretion.

Although no hard evidence for this suggestion is presented, it is supported by the finding that administration of metiamide to rats is ineffective in blocking pentagastrin-stimulated DNA-synthesis by the gastric mucosa (14).

Basal gastric acid secretion did not markedly change in cases 1 and 3 and histamine H_2-receptor antagonists were found to be effective in a more or less dose-dependent manner. Our results contrast with those of Bonfils et al (9) who found partial reduction in efficacy in one and total inefficacy in 5 cases during administration of histamine H_2-receptor antagonists for 15-190 days. Furthermore, we did not observe a so-called "prolonged inhibition" of gastric acid secretion after withdrawal of metiamide or cimetidine (15). Within 12 hours after withdrawal of the drug all 3 patients experienced a recurrence of diarrhea and gastric acid secretion was not found to be markedly reduced 36 hours after discontinuing the drug.

Bonfils et al (9) also found that secretin was no longer capable of increasing serum gastrin levels in 2 out of 5 Zollinger-Ellison patients on treatment with histamine H_2-receptor antagonists. In our 3 Zollinger-Ellison patients on long-term treatment, neither the fasting serum gastrin level nor the serum gastrin response to secretin changed markedly (table 1).

The clinical efficacy of the histamine H_2-receptor antagonists was excellent in cases 2 and 3. The efficacy of cimetidine in case 1 was difficult to assess since this patient had concomitant pancreatic insufficiency. Metiamide was clinically effective, however, before the onset of pancreatitis and also during pancreatic insufficiency cimetidine markedly reduced diarrhea in this patient. Although the diagnosis of pancreatitis was made during treatment with histamine H_2-receptor antagonists, we do not believe that this disorder was related to the drugs used. Co-existing abnormalities, such as hyperparathyroidism,gallbladder disease or pancreatic tumors, might have been involved in the pathogenesis of pancreatitis in this patient. Moreover, serum and urinary levels of amylase were repeatedly normal in the 2 other Zollinger-Ellison patients on long term treatment.

None of our patients had gynecomastia, galactorrhea or increased serum prolactin concentrations, as have been found by others (16-18). No adverse reactions of an immunological nature, as suggested previously (19), could be demonstrated by detailed immunological studies.

In conclusion, histamine H_2-receptor antagonists were effective in the long-term symptomatic treatment of our Zollinger-Ellison patients, without side-effects. Although it is clear that more patients have to be studied for

longer periods, our results show that long term treatment with histamine H_2-receptor antagonists may be a valuable alternative therapy for total gastrectomy in the Zollinger-Ellison syndrome.

Addendum

At present, (January,1980) cimetidine is still effective in all 3 cases.

Acknowledgments

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References

1 THJODLEIFSSON B, WORMSLEY KG: Aspects of the effect of metiamide on pentagastrin-stimulated and basal gastric secretion of acid and pepsin in man. Gut 16: 501, 1975

2 HALLORAN LG, SWANK M, HAYNES BW: Metiamide in Zollinger-Ellison syndrome (letter). Lancet 1: 281, 1975

3 MAINARDI M, MAXWELL V, STURDEVANT AL et al: Inhibition of gastric acid secretion by metiamide in Zollinger-Ellison syndrome. Am J Dig Dis 20: 280, 1975

4 BLAIR EL, GRUND ER, MILLER IT et al: Metiamide in the Zollinger-Ellison syndrome. Am J Dig Dis 20: 1123, 1975

5 BONFILS S, BERNIER JJ, MIGNON M et al: Syndrome de Zollinger-Ellison traité médicalement par un inhibiteur des récepteurs H_2 à l'histamine. Nouv Presse Méd 4: 2377, 1975

6 RICHARDSON CT, WALSH JH: The value of a histamine H_2-receptor antagonist in the management of patients with the Zollinger-Ellison syndrome. N Engl J Med 294: 133, 1976

7 STAGE JG, STADIL F, RUNE S et al: Treatment of Zollinger-Ellison patients with cimetidine (abstract). Scand J Gastroenterol 11 (suppl 41):75, 1976

8 ORCHARD JL, PETERNEL WW: Cimetidine therapy in Zollinger-Ellison syndrome. JAMA 237: 2221, 1977

9 BONFILS S, MIGNON M, KLOETI G et al: Therapeutic assessment of histamine H_2 blockers in 10 cases of Zollinger-Ellison syndrome (abstract).Gastroenterology 72: 813, 1977

10 McCARTHY DM, OLLINGER EJ, MAY RJ et al: Long term therapy of Zollinger-Ellison syndrome with H_2-histamine receptor blocking agents (abstract). Gastroenterology 72: 1162, 1977

11 HECTOR RM: Improved technique of gastric aspiration. Lancet 1: 15, 1968

12 LAMERS CBH, VAN TONGEREN JHM: Comparative study of the value of the calcium, secretin, and meal stimulated increase in serum gastrin to the diagnosis of the Zollinger-Ellison syndrome. Gut 18: 128, 1977

13 DE PAUW B, LAMERS C, WAGENER D et al: Immunological studies after long-term H_2-receptor antagonist therapy. (Letter) Lancet 2: 616, 1977

14 JOHNSON LR, GUTHRIE PD: Secretin inhibition of gastrin-stimulated deoxyribonucleic acid synthesis. Gastroenterology 67: 601, 1974

15 BONFILS S, MIGNON M, JIAN R et al: Biological studies during long-term cimetidine administration in Zollinger-Ellison syndrome. In: Cimetidine, eds. Burland WL, Simkins MA. Amsterdam, Excerpta Medica 1977, p 311.

16 HALL WH: Breast changes in males on cimetidine (letter). N Engl J Med 295: 841, 1976

17 SHARPE PC, HAWKINS BW: Efficacy and safety of cimetidine. Long-term treatment with cimetidine. In: Cimetidine, eds Burland WL, Simkins MA. Amsterdam, Excerpta Medica 1977, p 358

18 DELLE FAVE GF, TAMBURRANO G, DE MAGISTRIS L et al: Gynaecomastia with cimetidine (letter). Lancet 1: 1319, 1977

19 Cimetidine, publicity, and safety (editorial). Lancet 1: 129, 1977

CHAPTER 6

EFFECT OF ONE YEAR TREATMENT WITH CIMETIDINE ON GASTRIN CELL FUNCTION AND ON PARIETAL CELL FUNCTION AND ITS SENSITIVITY TO CIMETIDINE

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Abstract

Twenty-two duodenal and 16 gastric ulcer patients were treated with 400 mg cimetidine twice daily for one year after their ulcers had healed. No change in gastric acid secretion was observed before and after treatment in 20 duodenal and 13 gastric ulcer patients. Similarly, the inhibitory effect of 200 mg cimetidine on gastric acid secretion was unaltered in 11 duodenal and 6 gastric ulcer patients studied, and cimetidine blood levels were unchanged in 9 duodenal and 4 gastric ulcer patients after this year. In 7 duodenal and 6 gastric ulcer patients the serum gastrin response to a standard test meal before and after treatment was identical.Four duodenal ulcer patients and 3 gastric ulcer patients had endoscopically proven relapse ulceration. At endoscopy after one year treatment no asymptomatic ulcers were found in 18 duodenal and 13 gastric ulcer patients. It is concluded that long term treatment with cimetidine influences neither gastrin cell function nor parietal cell function nor its sensitivity to cimetidine in duodenal and gastric ulcer patients.

Introduction

Treatment with cimetidine is effective in duodenal ulcer disease (1,2,3). There is additional proof that maintenance treatment with low dose cimetidine prevents duodenal ulcer relapse (4-9). In the prevention of gastric ulcer relapse cimetidine seems equally effective (10,11). However, before maintenance treatment with cimetidine in peptic ulcer disease can be advocated, the safety of such treatment has to be ascertained. Although treatment with cimetidine for short periods of time seems to be safe, side effects and after effects of such treatment on parietal and gastrin producing cells may become overt only during long term treatment. Furthermore, it has to be demonstrated that the metabolism of cimetidine does not change with time resulting in lower blood levels of cimetidine and less inhibition of gastric acid secretion. In duodenal ulcer patients some of these aspects have been studied (9,12-16). In gastric ulcer patients, however, no studies of this kind have yet been done.

This study was undertaken to assess the effect of one year continuous treatment with cimetidine on gastrin cell function, as determined by postprandial serum gastrin levels, and on parietal cell function, as assessed by basal and pentagastrin stimulated gastric acid secretion in duodenal and gastric ulcer patients. Furthermore the inhibition of gastric acid secretion by cimetidine in relation to the blood cimetidine concentrations was studied

before and after one year treatment. Finally, data on re-ulceration, side effects and endoscopy of asymptomatic patients after one year of treatment are presented.

Patients and methods

Thirty-eight peptic ulcer patients without prior gastric operation were studied; 22 had a duodenal and 16 had a gastric ulcer. One duodenal ulcer and 7 gastric ulcer patients were females. Mean age in duodenal ulcer patients was 48 ± 4 year and in gastric ulcer patients 51 ± 3 year (mean ± SE). All patients had endoscopically proven healed ulcers before they started maintenance treatment. Treatment with 400 mg cimetidine after breakfast and 400 mg at bedtime was continued for one year. The patients were not allowed to use any other drug with known or supposed ulcerogenic properties and no antacids were used. The patients were not encouraged to change their smoking and drinking habits during the trial and no dietary advice was given. Patients were seen at bi-monthly intervals and at each visit a careful history was taken of ulcer symptoms and possible side effects. Further, blood was drawn for laboratory tests: haemoglobin, haematocrit, total and differential white blood cell counts, platelets, serum creatinine, alkaline phosphatase, SGOT and SGPT, and an urinalysis was performed. To test patient compliance at each visit a urine sample was examined on the presence of cimetidine. The detection of cimetidine in urine was carried out by thin layer chromatography (Smith, Kline and French laboratories, Welwyn Garden, England: personal communication). In case of relapse symptoms endoscopy was performed. Patients with relapse ulcers discontinued maintenance treatment with cimetidine and were treated as judged appropriate. After one year treatment all remaining patients were re-endoscoped and treatment was stopped. Immediately before they started cimetidine treatment several tests were undertaken in a number of patients. These tests were repeated one year later between 3 and 7 days after cimetidine had been stopped. At repeat tests for gastric acid secretion and serum gastrin concomitant blood cimetidine levels were assessed: these were all below the detection limit (<0.05 µg/ml).

- Gastric analysis was performed in 20 duodenal and 13 gastric ulcer patients. After an overnight fast a gastric tube was positioned according to the method as described by Hector (17). Four 15 minute basal secretory collections were obtained and subsequently four 15 minute samples were collected after injection of pentagastrin (6 µg/kg i.m.). Peak acid output was calcu-

lated as the sum of the 2 consecutive highest 15 minute samples multiplied by 2. Hydrogen ion concentration (mmol H^+/l) was determined by titration with 0.1 N NaOH up to pH 7.0.

- Gastric acid secretion after cimetidine was determined in 11 duodenal and 6 gastric ulcer patients. One hour after oral intake of 200 mg cimetidine gastric analysis was performed as described above although here basal secretion was measured during two 15 minute periods. This 30 minute result was multiplied by 2 in order to express as mmol H^+/hour.

- Blood cimetidine concentrations were measured in 9 duodenal and 4 gastric ulcer patients. Venous blood samples were drawn 60, 90, 105 and 135 minutes after oral intake of 200 mg cimetidine during gastric analysis. Heparinized whole blood was stored at -20°C and cimetidine concentrations were determined by high pressure liquid chromatography as described by Randolph et al (18). Minimal detectable blood concentration by this method was 0.05 µg/ml. All samples were assessed twice.

- Serum gastrin levels were measured in 7 duodenal and 6 gastric ulcer patients. Levels were determined before breakfast and 15, 30, 45, 60, 90, and 120 minutes after a test meal. This test meal consisted of one slice of white bread, 50 g cheese,one boiled egg,200 ml skimmed milk, containing in total: 30 g protein, 20 g fat and 24 g carbohydrate. The integrated gastrin response (IGR) was calculated by determining the area under the curve of the gastrin concentrations after subtraction of the basal concentration. Pre-treatment samples were stored at -20°C and were analysed together with post-treatment samples in the same assay to avoid interassay variation. Serum gastrin levels were measured by radio-immunoassay using a rabbit antiserum (19,20). This antiserum raised against human gastrin I, 2-17 covalently coupled to bovine serum albumin, binds all known C-terminal gastrin components with an almost equimolar potency (21). In 137 normal subjects the serum gastrin level was 39 $\pm$ 15 pg/ml (mean $\pm$ 1 SD) (range 10-86 pg/ml).

For statistical analysis Wilcoxon's signed rank test for matched pairs and Mann Whitney U test were used as appropriate.

Results

Patient compliance

No patient failed to attend any of the follow-up visits during maintenance

treatment. Bi-monthly urine cimetidine checks were, with 14 exceptions (6%), in different patients, all positive.

Gastric acid secretion and its inhibition by cimetidine

There was no difference between the pre- and post-treatment data neither in duodenal nor in gastric ulcer patients (fig 1).

Serum gastrin

In duodenal ulcer patients the fasting and meal stimulated serum gastrin levels before and after one year of treatment were not significantly different; the fasting levels being 42 ± 5 and 47 ± 5 pg/ml (mean ± SE; ns) and the integrated gastrin response 5.8 ± 0.8 and 6.1 ± 1.4 ng/ml.120 min (mean ± SE; ns) respectively. In gastric ulcer patients the fasting serum gastrin level before treatment was 42 ± 7 pg/ml and after 58 ± 11 pg/ml (mean ± SE; ns); the integrated gastrin responses were 6.4 ± 1.2 and 7.0 ± 1.3 ng/ml.120 min (mean ± SE; ns) (fig 2).

Blood cimetidine levels

There was no difference between the data of the duodenal and the gastric ulcer patients studied and so they were pooled. The mean cimetidine blood level between 60 and 135 minutes after oral intake of 200 mg before treatment was 0.83 ± 0.08 µg/ml and after one year 0.88 ± 0.08 µg/ml (mean ± SE). Mean peak blood levels were 1.05 ± 0.10 and 1.11 ± 0.10 µg/ml (mean ± SE) respectively. None of the differences between pre- and post-treatment blood cimetidine levels were statistically significant (fig 3).

Relapse ulcers

During maintenance treatment 4 duodenal ulcer patients (18%) and 3 gastric ulcer patients (19%) suffered a relapse of ulcers as proven by endoscopy. Gastric acid secretion measured before treatment in relapse patients was not significantly different from non-relapse patients. Six relapse patients studied (3 with a duodenal and 3 with a gastric ulcer) showed no decreased inhibition of acid secretion 60 to 150 min after oral intake of cimetidine compared to inhibition of acid secretion in 15 patients who did not relapse (fig 4).

Side effects and laboratory effects

During treatment no side effects were reported. On laboratory screening only minor transient changes outside normal were identified.

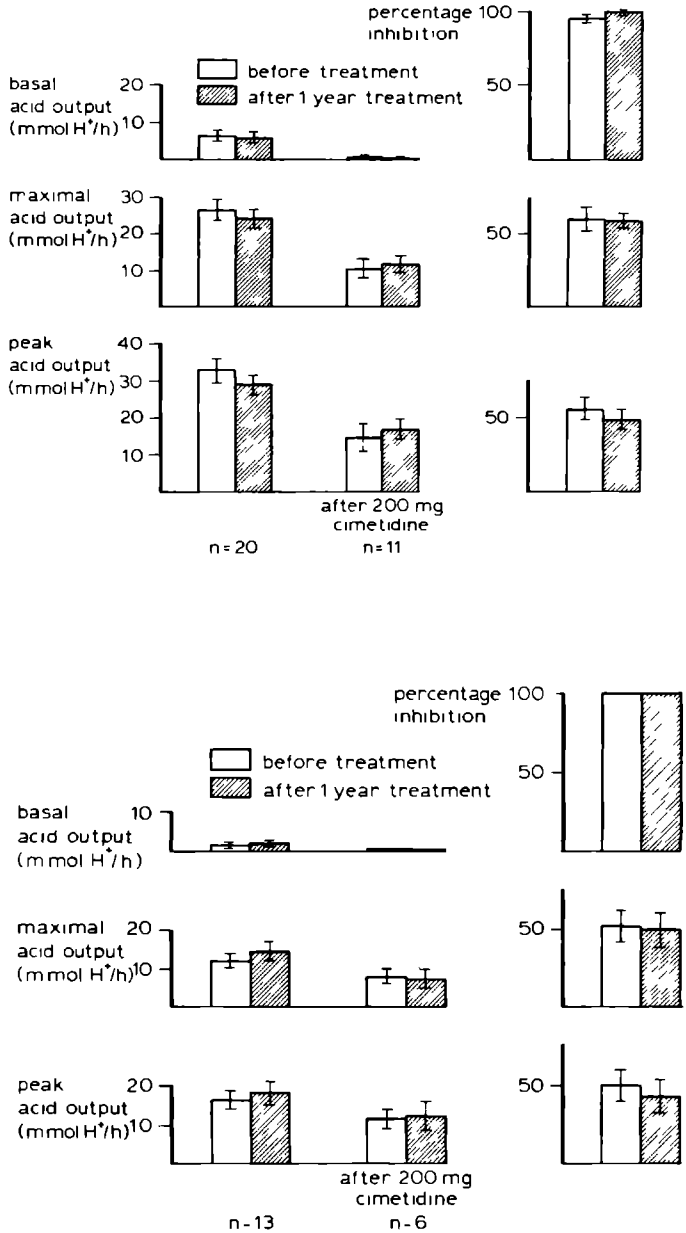

Fig 1 Gastric acid secretion, gastric acid secretion after 200 mg cimetidine (mmol H^+/h; mean ± SE) and resulting percentage of secretion inhibition (mean ± SE) before and after one year treatment with cimetidine in duodenal (upper panel) and gastric ulcer patients (lower panel).

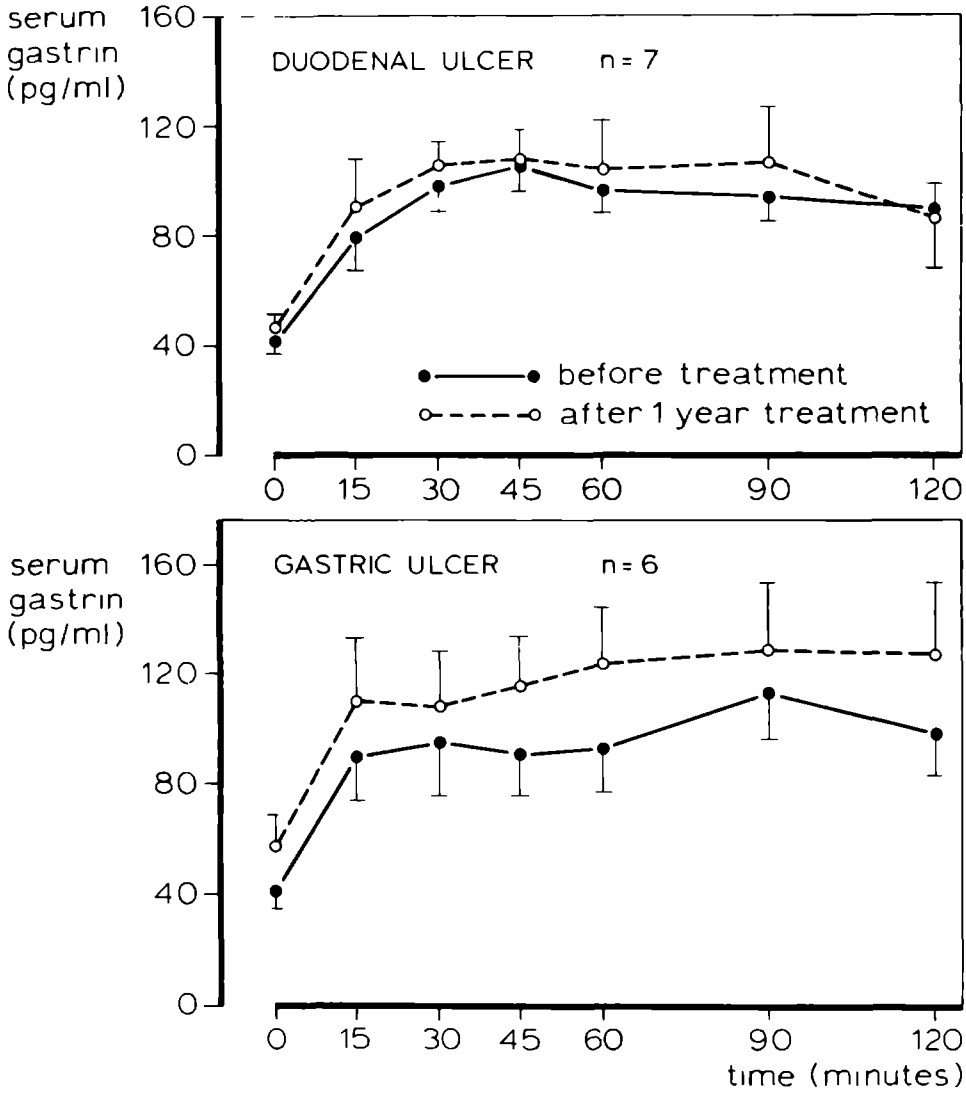

Fig 2 Serum gastrin levels (pg/ml; mean ± SE) fasting and in response to a test meal before and after one year treatment with cimetidine in 7 duodenal (top panel) and 6 gastric ulcer patients (bottom panel).

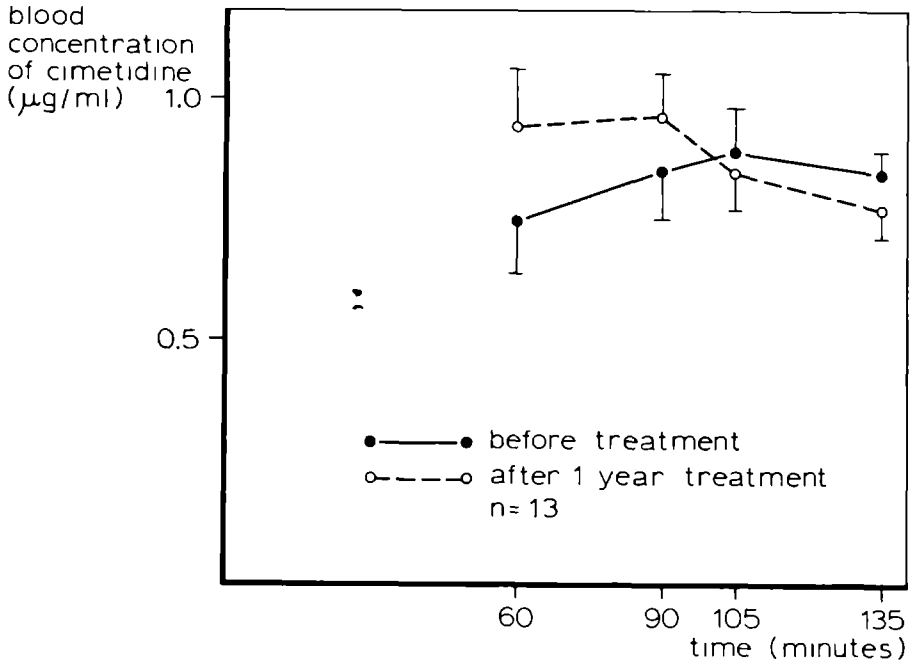

Fig 3 Blood cimetidine concentrations (μg/ml; mean ± SE) after 200 mg cimetidine orally before and after one year treatment with cimetidine in 13 patients.

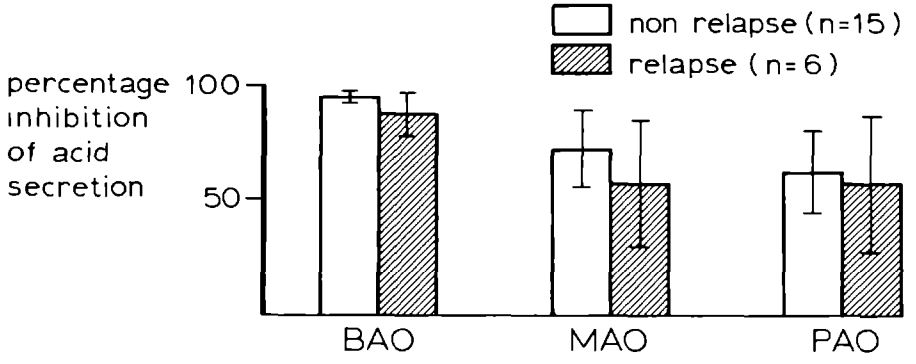

Fig 4 Percentage of inhibition of gastric acid secretion (mean ± SE) by 200 mg cimetidine orally before treatment in 15 non-relapse and 6 relapse patients.

Repeat endoscopy

Repeat endoscopy after one year treatment in 18 duodenal and 13 gastric ulcer patients who did not suffer a symptomatic relapse revealed no ulcers.

Discussion

The present study shows that one year treatment with cimetidine does not influence gastric acid secretion. Other investigators reported similar findings in duodenal ulcer patients (4,13,16). This study shows that gastric acid secretion in gastric ulcer patients is also unaltered. Whatever mechanism causes the relative hyposecretion of gastric acid in gastric ulcer patients, it was unchanged after one year treatment with cimetidine while the ulcer remained healed. The basal and postprandial serum gastrin levels in duodenal and gastric ulcer patients were not influenced by one year treatment with cimetidine. So far other reports on serum gastrin in duodenal ulcer patients after the long term use of cimetidine have been conflicting (12,14,16). There are no other reports on serum gastrin in gastric ulcer patients after the long term use of cimetidine.

It might be assumed that possible after-effects of long term cimetidine treatment on gastrin cell function and on parietal cell function will become manifest earlier in gastric ulcer patients than in duodenal ulcer patients due to the significantly lower gastric acid secretion after cimetidine in these patients (3). Such an effect, however, was not demonstrated in either group of patients. Cimetidine remained effective during one year continuous treatment: blood levels of cimetidine and inhibition of gastric acid secretion were unchanged.

There was no reduced inhibition of gastric acid secretion in patients who suffered a relapse ulcer during maintenance treatment compared to patients who did not relapse.

Rune et al (22) could also not demonstrate a relation between inhibition of acid secretion, blood cimetidine concentration and symptomatic effectiveness of cimetidine during short term treatment.

In conclusion: maintenance treatment with cimetidine for one year in duodenal and gastric ulcer patients was safe. No after effects or rebound phenomena after stopping the treatment were observed. The acid inhibitory effect of cimetidine did not change.

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References

1 BODEMAR G, WALAN A: Cimetidine in the treatment of active duodenal and prepyloric ulcers. Lancet 2: 161, 1976

2 BINDER HJ, COCCO A, CROSSLEY RJ et al: Cimetidine in the treatment of duodenal ulcer. A multicenter double blind study. Gastroenterology 74: 380, 1978

3 FESTEN HPM, LAMERS CBH, VAN TONGEREN JHM: De onderdrukking van de maagzuurproductie door middel van cimetidine: resultaten van een dubbelblind onderzoek naar de betekenis van cimetidine voor de behandeling van peptische ulcera. Nederlands Tijdschrift voor Geneeskunde 122: 862, 1978

4 BODEMAR G, WALAN A: Maintenance treatment of recurrent peptic ulcer by cimetidine. Lancet 1: 403, 1978

5 BLACKWOOD WS, MAUDGAL DP, NORTHFIELD TC: Prevention by bedtime cimetidine of duodenal ulcer relapse. Lancet 1: 626, 1978

6 BURLAND WL, HAWKINS BW, HORTON RJ et al: The longer term treatment of duodenal ulcer with cimetidine. In: Cimetidine: Proceedings of the Westminster Hospital Symposium 1978. Edited by C Wastell, P Lance, Churchill-Livingstonse; Edinburgh, London and New York 1978, p 66

7 GRAY GR, SMIT IS, MACKENZIE I et al: Long term cimetidine in the management of severe duodenal ulcer dyspepsia. Gastroenterology 74: 397, 1978

8 GUMAND-HØYER E, BIRGER-JENSEN K, KRAG E: Prophylactic effect of cimetidine in duodenal ulcer disease. Brit Med J 1: 1095, 1978

9 HETZEL DJ, HANSKY J, SHEARMAN DJC et al: Cimetidine treatment of duodenal ulceration. Short term clinical trial and maintenance study. Gastroenterology 74: 389, 1978

10 MACHELL RJ, CICLITIRA PJ, FARHTING MJG et al: Cimetidine in the prevention of gastric ulcer relapse. Postgraduate Medical Journal 55: 393, 1979

11 BIRGER-JENSEN K, MØLMANN KM, RAHBEK I et al: Prophylactic effect of cimetidine in gastric ulcer patients. Scand J Gastroent 14: 175, 1979

12 SEWING KF, HAGIE L, IPPOLITI AF et al: Effect of one month treatment with cimetidine on gastric secretion and serum gastrin and pepsinogen levels. Gastroenterology 74: 376, 1978

13 SPENCE RW, CELESTIN LR, Mc CORMICK DA et al: The effect of long term treatment with cimetidine on gastric acid secretion and gastric response in man. In: Cimetidine: Proceedings of an International Symposium on Histamine H_2-receptor Antagonists. Edited by W Creutzfeldt, Excerpta Medica, Amsterdam-Oxford 1978, p 116

14 SPENCE RW, Mc CORMICK DA, ILIVER JM et al: The effect on serum gastrin of withdrawal of cimetidine after one year's treatment. In: Cimetidine: Proceedings of the Westminster Hospital Symposium 1978. Edited by C Wastell, P Lance, Livingstone, Edinburgh, London and New York 1978, p 153

15 BODEMAR G, NORLANDER B, FRANSSON L et al: The absorption of cimetidine before and during maintenance treatment with cimetidine and the influence of a meal on the absorption of cimetidine. Studies in patients with peptic ulcer disease. Br J Clin Pharmac 7: 23, 1979

16 FORREST JAM, FETTES M, Mc LOUGHLIN G et al: The effect of long term cimetidine on gastric acid secretion, serum gastrin and gastric emptying. Gut 20: 404, 1979

17 HECTOR RM: Improved technique of gastric aspiration. Lancet 1: 15, 1968

18 RANDOLPH WC, OSBORNE VL, WALKENSTEIN SS et al: High pressure liquid chromatographic analysis of cimetidine, a histamine H_2-receptor antagonist, in blood and urine. J Pharm Sci 66: 1148, 1977

19 REHFELD JF, STADIL F, RUBIN B: Production and evaluation of antibodies for the radioimmunoassay of gastrin. Scand J of Clin and Lab Invest 30: 221, 1972

20 LAMERS CBHW: Some aspects of the Zollinger-Ellison syndrome and serum gastrin. Thesis, Nijmegen 1976

21 REHFELD JF, STADIL F, MALMSTRØM J et al: Gastrin heterogeneity in serum and tissue. In: Gastrointestinal Hormones. Edited by JC Thompson, University of Texas press: Austin 1975, p 43

22 RUNE SJ, HESSELFELDT P, LARSEN NE: Clinical and pharmacological effectiveness of cimetidine in duodenal ulcer patients. Scand J Gastroent 14: 489, 1979

CHAPTER 7

IS DETERMINATION OF BLOOD CIMETIDINE LEVELS CLINICALLY RELEVANT?

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Abstract

Blood cimetidine levels were measured up to 5 hours after oral intake of 200 mg cimetidine with breakfast in 13 duodenal, 5 gastric and 15 anastomotic ulcer patients. There were large inter-individual differences in results. The mean peak blood concentration was 1.14±0.07 µg/ml (range 0.54-1.94 µg/ml), the mean period during which the blood concentration exceeded 0.5 µg/ml was 141±11 minutes (range 23-306 min) and the mean area under the cimetidine blood concentration curve (AUC) was 166±8 $\mu g.min.ml^{-1}$ (range 96-280 $\mu g.min.ml^{-1}$). Coefficient of variation of these parameters was 33%, 43% and 29% respectively. There were no significant differences in these parameters between non-operated patients and patients with a partial gastrectomy. In patients restudied after 2 to 5 months blood cimetidine levels proved well reproducible; mean coefficient of variation of peak blood level was 8.5±2.4%, of time during which blood levels exceeded 0.5 µg/ml 7.6±2.5%, and of the AUC 5.0±1.0%.

There was no difference in peak blood levels, duration of blood level exceeding 0.5 µg/ml and blood cimetidine AUC between patients healed after 4 weeks cimetidine therapy and those who took longer to heal. Likewise, there was no evidence of lower blood cimetidine concentrations in patients who relapsed during maintenance cimetidine treatment compared with those who did not relapse.

In conclusion: between-subject variations of cimetidine blood concentration are large and intra-individual reproducibility of blood levels is good. Cimetidine blood levels, however, do not correlate with the outcome of treatment with this drug in peptic ulcer patients.

Introduction

Cimetidine is effective in short and long term treatment of duodenal ulcer (1,2,3) and recurrent ulcer after partial gastrectomy (4). In the treatment of gastric ulcer the effect of cimetidine is less obvious (5). Even in duodenal and recurrent ulcer after partial gastrectomy, however, not all patients benefit equally from cimetidine therapy: after 8 weeks of treatment the ulcers in about 15 per cent of the patients do not heal (1,2) and the same percentage of patients suffer relapse ulceration during one year maintenance treatment with cimetidine (3,4). The effect of cimetidine on ulcer healing is probably entirely to be attributed to its gastric acid inhibitory capacity. According to several studies the inhibition of gastric acid secretion is directly related to the blood concentration of cimetidine

(6,7,8). Other studies have shown that between-subject variations of cimetidine blood levels are considerable (9-12). This variation in blood cimetidine levels, therefore, might influence the clinical response to treatment with cimetidine.

The aim of this study was to assess the between-subject variability and the within-subject reproducibility of blood cimetidine levels. Furthermore, the usefulness of measurement of blood cimetidine levels to predict the outcome of treatment with cimetidine was studied. This was done by retrospective analysis of the relation between the blood cimetidine levels and the response to short and long term cimetidine treatment in unoperated peptic ulcer patients and in patients with anastomotic ulcer after partial gastrectomy.

Patients and methods

Thirty-three patients with peptic ulcer disease were studied. Five patients had a gastric ulcer, 13 a duodenal ulcer and 15 a recurrent ulcer after partial gastrectomy. These patients formed part of a group who approximately 2 years prior to this investigation had been studied. At that time they were treated with cimetidine (1 g daily for 4 weeks) in double blind and, if necessary, subsequent open treatment courses until the ulcer had healed (4,13). Thereafter all these patients entered open maintenance treatment with 400 mg cimetidine twice daily for one year. Of this group those patients available were selected who had not healed after 4 weeks treatment and those who suffered a relapse ulcer during maintenance treatment. A control group was randomly selected from patients who healed within 4 weeks and did not relapse.

In none of the patients renal function was impaired: serum creatinine levels were within normal limits in all patients (<100 µmol/l).

After an overnight fast blood cimetidine levels were measured before and at 30, 60, 90, 120, 180, 240 and 300 minutes after ingestion of a 200 mg cimetidine tablet together with a standard breakfast. Whole blood cimetidine concentration was measured by high pressure liquid chromatography as described by Randolph et al (14). Minimum detectable blood level by this method was 0.05 µg/ml. The intra-assay precision, determined by the coefficient of variation of fivefold measurements of 3 blood samples with mean cimetidine concentrations of 0.24, 0.77 and 1.26 µg/ml, varied from 2.1 to 3.7%. The inter-assay coefficient of variation ranged from 2.1 to 7.0% for 4 consecutive determinations of 3 blood samples with mean cimetidine concentrations of 0.24, 0.71 and 1.14 µg/ml.

Peak blood level, the time during which the blood concentration exceeded 0.5 µg/ml and the area under the cimetidine blood concentration curve (AUC) were determined. Inter-individual variation for all these parameters was calculated and this calculation was also made after these data had been corrected for bodyweight and body surface area. Besides the correlation between the AUC and age was computed.

To assess the intra-individual variation of cimetidine concentrations blood levels were remeasured 2 to 5 months later in 7 out of the non-operated and 4 out of the patients with a partial gastrectomy according to the same protocol.

Furthermore, cimetidine blood levels in 12 non-operated patients were correlated with those obtained approximately 2 years prior to this study with a slightly different protocol. At that time blood concentrations were measured at 0, 60, 90, 105 and 135 min after 200 mg cimetidine on a fasting stomach.

Two duodenal, 2 gastric and 5 anastomotic ulcer patients had not healed after 4 weeks cimetidine treatment and were designated as "non responders". All other patients responded to 4 weeks therapy. Blood cimetidine levels in non-responding patients were compared with those in "responders". Four duodenal, 1 gastric and 4 anastomotic ulcer patients suffered a relapse ulcer during maintenance cimetidine treatment. Blood cimetidine levels in relapse patients were compared with those in patients who did not relapse.

Inter-individual variation was expressed as the coefficient of variation. Intra-individual reproducibility was expressed as the mean of the coefficients of variation calculated for the 2 consecutive measurements in each patient. Regression analysis was done by the method of least squares.

Comparison between groups was performed by Student's t-test. Data are presented as the mean $\pm$ 1 SEM.

Results

Mean peak blood cimetidine concentration in non-operated patients was 1.13 ± 0.08 µg/ml (range 0.54-1.80 µg/ml; n=18). This level was reached 60 minutes (range 30-120 min) after oral intake of the drug. In patients with a partial gastrectomy mean peak blood level was 1.15 ± 0.10 µg/ml (range 0.58-1.94 µg/ml; n=15) and this level occurred also after 60 minutes (range 30-180 min). Mean duration of blood level exceeding 0.5 µg/ml was 145 ± 15 min (range 23-306 min) in non-operated patients and 137 ± 14 min (range 58-271

min) in patients with a partial gastrectomy. Mean area under the blood concentration curve in non-operated patients was 171±12 μg.min.ml^{-1} (range 96-280 μg.min.ml^{-1}) and in patients with a partial gastrectomy 161±11 μg.min.ml^{-1} (range 98-263 μg.min.ml^{-1}) (fig 1).

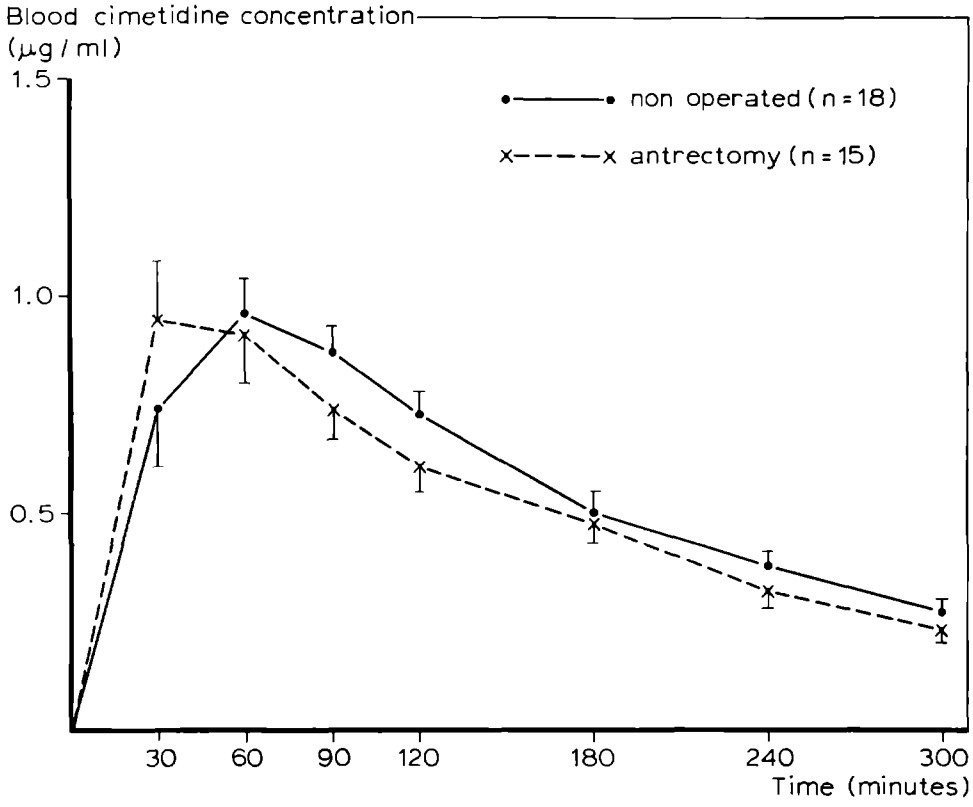

Fig 1 Blood cimetidine concentration (mean ± 1 SEM) after 200 mg cimetidine orally with breakfast in patients without gastric operation and patients with a partial gastrectomy.

None of the differences between non-operated and antrectomized patients were statistically significant. The coefficient of variation was therefore calculated for the patients as one group. The coefficient of variation of peak blood level was 33%, of period of blood level exceeding 0.5 μg/ml 43% and of AUC 29%. If correction for bodyweight was made these coefficients of varia-

tion were respectively: 34%, 36% and 28%, and corrected for body surface area they were 32%, 34% and 25% respectively.

Correlation coefficient (r) of AUC with age was 0.40 ($p<0.05$).

Cimetidine blood levels measured on 2 different occasions in non-operated patients and in patients with a partial gastrectomy were well reproducible. The mean coefficient of variation of the 2 determinations of peak blood levels was 8.5±2.4%, of period of blood levels exceeding 0.5 µg/ml 7.6±2.5% and of the area under the cimetidine blood concentration curve 5.0±1.0%. Correlation coefficient (r) of the 2 measurements of peak blood level was 0.91 ($p<0.001$); of duration of blood concentration exceeding 0.5 µg/ml 0.96 ($p<0.001$) and of AUC 0.97 ($p<0.001$). The AUC measured on these 2 different occasions is presented in figure 2.

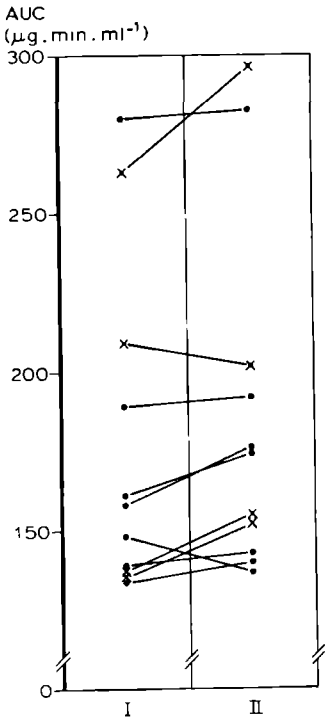

Fig 2 *Area under the blood cimetidine curve* (AUC, µg.min.ml^{-1}) measured on 2 different occasions (I and II) in 4 patients with a partial gastrectomy (x) and 7 non-operated patients (•).

Correlation coefficient (r) of AUC in the 12 patients measured in this study and 2 years earlier was 0.77 ($p<0.01$).

Peak blood level, period of blood level exceeding 0.5 µg/ml and area under

the blood concentration curve in patients with different clinical reaction to cimetidine therapy are given in table 1. There were no significant differences between responding and non-responding or relapsing and non-relapsing patients without previous gastric surgery. Likewise if data from duodenal and gastric ulcer patients were evaluated as separate groups, no significant differences were seen. In patients with a partial gastrectomy there was no difference in peak blood level, period of blood cimetidine concentration exceeding 0.5 µg/ml and AUC between responding and non-responding patients. In relapse patients these data were significantly higher than in non-relapse patients ($p<0.01$).

Discussion

This study confirms that blood cimetidine levels are highly variable in different individuals (9-12). The most variable parameter was the period during which the blood cimetidine concentration exceeded 0.5 µg/ml. According to several studies 0.5 µg/ml is the blood concentration required to achieve 50% inhibition of maximal acid output (7,15).

Increase in bioavailability of cimetidine with age has been reported (10, 16). In our study correlation of AUC with age reached just statistical significance. Age, however, accounts only partly for the large variations measured. Disparities to the same extent were also present in age contemporaries. From this study we cannot conclude what other factors cause these differences. The variations persisted after correction for body weight or body surface area.

We did not find differences in cimetidine blood levels, period of cimetidine blood concentration exceeding 0.5 µg/ml and time of occurrence of peak blood level between patients with an intact stomach and patients with a partial gastrectomy. Partial gastrectomy, therefore, does not affect the absorption of cimetidine.

Cimetidine blood levels studied twice with 2 to 5 months interval were very well reproducible in non-operated patients as well as in patients with a partial gastrectomy. Moreover, if compared to blood levels assessed 2 years earlier cimetidine concentrations were in the same range. This shows that within-subject reproducibility of blood cimetidine levels is good.

On this basis we felt justified to evaluate the relation between data on blood cimetidine levels measured in this study and previous reaction to cimetidine therapy. No such correlation was found: peak blood levels, time during which the blood level exceeded 0.5 µg/ml and AUC were not lower in non-respon-

Table 1 PEAK BLOOD CONCENTRATION, PERIOD OF BLOOD LEVEL EXCEEDING 0.5 µG/ML, AND AREA UNDER THE BLOOD CIMETIDINE CONCENTRATION CURVE IN PATIENTS WITH DIFFERENT CLINICAL REACTION TO THERAPY

	Responders	Non-responders	p	Non-relapse	Relapse	p
Non-operated patients:	n=14	n=4		n=13	n=5	
peak blood concentration (µg/ml)	1.11±0.10	1.21±0.15	ns*	1.14±0.10	1.11±0.17	ns
period exceeding 0.5 µg/ml (min)	145±18	143±30	ns	146±13	143±46	ns
area under the curve ($\mu g.min.ml^{-1}$)	177±16	176±31	ns	171±13	172±29	ns
Antrectomized patients:	n=10	n=5		n=11	n=4	
peak blood concentration (µg/ml)	1.14±0.12	1.17±0.22	ns	0.98±0.09	1.63±0.14	p<0.01
period exceeding 0.5 µg/ml (min)	143±13	127±37	ns	116±11	197±31	p<0.01
area under the curve ($\mu g.min.ml^{-1}$)	166±10	152±29	ns	140±7	219±15	p<0.01

*ns = statistically not significantly different

All data are presented as the mean ± 1 SEM

ding or relapse patients. We have no explanation why blood levels in relapse patients with a partial gastrectomy were higher than in non-relapse patients. From this study we cannot conclude whether the amount of inhibition of gastric acid secretion achieved by cimetidine correlates with clinical response to therapy because inhibition of acid secretion was not measured. However, there are several observations that inhibition of gastric acid secretion by cimetidine correlates well with the blood cimetidine concentration (6,7,8). Yet, in one study no such correlation was found (12). In that study also no correlation was observed between the symptomatic effect of cimetidine therapy and the inhibition of gastric acid secretion or cimetidine blood levels (12).

We conclude that within-subject reproducibility of cimetidine blood levels is good in patients with an intact stomach as well as in patients after a partial gastrectomy. Between-subject variation of cimetidine blood concentration, however, is large. Nevertheless measurement of cimetidine blood levels does not seem to be of clinical importance since there is no correlation between cimetidine concentrations and the outcome of treatment with cimetidine in peptic ulcer patients.

References

1 BODEMAR G, WALAN A: Cimetidine in the treatment of active duodenal and prepyloric ulcers. Lancet 2: 161, 1976

2 HETZEL DJ, HANSKY J, SHEARMAN DJC et al: Cimetidine treatment of duodenal ulceration. Short term clinical trial and maintenance study. Gastroenterology 74: 389, 1978

3 BURLAND WL, HAWKINS BW, HORTON RJ et al: The longer term treatment of duodenal ulcer with cimetidine. In: Cimetidine, proceedings of the Westminster Hospital Symposium 1978. Edited by: C Wastell and P Lance. Edinburgh-London and New York, Churchill Livingstone, 1978, p 66

4 FESTEN HPM, LAMERS CBH, DRIESSEN WMM et al: Cimetidine in anastomotic ulceration after partial gastrectomy. Gastroenterology 76: 83, 1979

5 GWYN MORGAN A, Mc ADAM WAF, PACSOO C et al: Cimetidine: an advance in gastric ulcer treatment? Br Med J 2: 1323, 1978

6 HENN RM, ISENBERG JI, MAXWELL V et al: Inhibition of gastric acid secretion by cimetidine in patients with duodenal ulcer. N Engl J Med 293: 371, 1975

7 POUNDER RE, WILLIAMS JG, RUSSELL RCG et al: Inhibition of food stimulated gastric acid secretion by cimetidine. Gut 17: 161, 1976

8 AADLAND E, BERSTAD A, SEMB LS: Inhibition of pentagastrin stimulated gastric secretion by cimetidine in healthy subjects. In: Cimetidine, proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by W Burland and M Simkins. Excerpta Medica Amsterdam-Oxford, 1977, p 87

9 BODEMAR G, NORLANDER B, FRANSSON L et al: The absorption of cimetidine before and during maintenance treatment with cimetidine and the influence of a meal on the absorption of cimetidine. Studies in patients with peptic ulcer disease. Br J Clin Pharmac 7: 23, 1979

10 REDOLFI A, BORGOGELLI E, LODOLA E: Blood levels of cimetidine in relation to age. Europ J Clin Pharmacol 15: 257, 1979

11 GRAHNEN A, VON BAHR C, LINDSTRÖM B et al: Bioavailability and pharmacokinetics of cimetidine. Eur J Clin Pharmacol 16: 335, 1979

12 RUNE SJ, HESSELFELDT P, LARSSEN NE: Clinical and pharmacological effectiveness of cimetidine in duodenal ulcer patients. Scand J Gastroent 14: 489, 1979

13 FESTEN HPM, LAMERS CBH, VAN TONGEREN JHM: De onderdrukking van de maagzuurproductie door middel van cimetidine: resultaten van een dubbelblind onderzoek naar de betekenis van cimetidine voor de behandeling van peptische ulcera. Ned T Geneesk 122: 862, 1978

14 RANDOLPH WC, OSBORNE VL, WALKENSTEIN SS et al: High pressure liquid chromatographic analysis of cimetidine, a histamine H_2-receptor antagonist in blood and urine. J Pharm Sci 66: 1148, 1977

15 BURLAND WL, DUNCAN WAM, HESSELBO T et al: Pharmacological evaluation of cimetidine, a new histamine H_2-receptor antagonist, in healthy man. Br J Clin Pharmac 2: 481, 1975

16 SOMOGYI A, ROHNER HG, GUGLER R: Pharmacokinetics and bioavailability of cimetidine in gastric and duodenal ulcer patients. Clin Pharmacokinetics 5: 84, 1980

CHAPTER 8

CIMETIDINE DOES NOT ACCELERATE SKIN GRAFT REJECTION IN MICE

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Abstract

The influence of cimetidine on skin graft rejection was studied in a well defined transplantation model of inbred mice. Four allogeneic transplantation combinations with increasing antigenic disparity and one xenograft combination were studied. Cimetidine (25 mg/kg body weight) was administered intraperitoneally at 8 hour intervals until rejection occurred. No differences in graft survival were observed between cimetidine-treated groups and saline-treated controls in any of the combinations studied.

Introduction

Cimetidine is a competitive antagonist of histamine on H_2-receptors. Its main effect is a marked inhibition of gastric acid secretion and therefore it is widely used in clinical practice. As T lymphocytes bear H_2-receptors (1-3) some concern has been raised about a possible influence of cimetidine on the immune response. Inhibition of suppressor T cells by cimetidine might result in an enhancement of delayed type hypersensitivity reaction, and some observations in vivo and in vitro support this hypothesis (4,5). Other studies, however, did not confirm these findings (6,7). The putative immunostimulatory effect of cimetidine is of considerable importance because cimetidine has been used successfully in the prevention of upper gastrointestinal haemorrhage in renal transplant recipients (8). The cellular immune response which plays an important role in renal allograft rejection, might be enhanced by treatment with cimetidine (9,10).

The availability of many inbred mouse strains makes it possible to study graft rejection in donor recipient combinations of well defined antigenic disparity. We have taken advantage of this situation and have studied the effects of cimetidine on skin graft survival in models with increasing antigenic differences.

Materials and methods

Mice

Inbred lines of B10.D2/New Sn, B10.A, B10.Br, C57B110, and B10.LP mice were originally obtained from the Jackson Laboratory, Bar Harbor, Maine, USA. Inbred PVG/c rats came originally from the Institute of Psychiatry, Bethlem Royal Hospital, Beckenham, Kent, U.K. These strains were kept by continuous brother-sister mating in our animal laboratory.

Donor-recipient combinations

Information concerning H-2 haplotypes and H-2 recombinants came from Festenstein and Demant (11) and concerning non-H-2 loci from Graff and Bailey (12). The 5 chosen combinations and their antigenic disparity are listed in table 1. They were chosen so as to represent an increase in histoincompatibility; i.e. a number of weak non-H-2 differences;an H-2D difference;an H-2K difference; a complete H-2 complex disparity and a xenogeneic difference.

Skin grafting technique

Donor tail skin was grafted onto the flank of the recipients by a modified "fitted graft" technique as described earlier (13). Skin grafts were inspected daily.

Drug administration

The recipients received intraperitoneal injections of 0.5 mg cimetidine dissolved in 0.1 ml saline (25 mg/kg body weight) at 8 hr intervals until the skin grafts were rejected. Control animals were similarly treated with 0.1 ml saline.

Statistics

Mean survival times in days were calculated for each group and differences between cimetidine and control groups were compared by Student's t-test.

Results

There was no difference in graft survival time between the cimetidine- and the saline-treated mice. Results for combinations with low antigenic disparity were not different from those for combinations with higher antigenic disparity (table 2).

Discussion

Rejection of skin grafts in the mouse is primarily a cellular phenomenon.Allogeneic and xenogeneic skin grafts in congenitally T cell-deficient, nude mice are accepted indefinitely (14,15), despite the fact that these mice are able to produce antibodies of both IgM and IgG class directed against the graft antigens (16). Skin graft experiments, therefore, offer the opportunity to study the influence of drugs on T cell function in vivo. Skin graft models are to be preferred because in the rejection of whole organ transplants humoral

Table 1 ANTIGENIC DIFFERENCES OF STRAIN COMBINATIONS STUDIED

Donor → Recipient	H-2 complex			Non-H-2-loci
	Haplotype	Specificities		
		private	public	
C57Bl10 → B10.LP	b → b	-	-	H-3; H-13 and probably two others(17)
B10.Br → B10.A	k → axb	H-2D.32	H-2.7	
B10.D2 → B10.A	d → axb	H-2K.31	H-2.34	
B10.D2 → C57Bl10	d → b	H-2K.31 H-2D.4	H-2.3,8,10,13,34,40, 41,42,43,44,47,49	
PVG/c → C57Bl10	xenogeneic graft			

Table 2 MEAN SKIN GRAFT SURVIVAL TIME IN CIMETIDINE AND SALINE TREATED GROUPS

Donor → Recipient	Mean survival time ± SD(days)		p*
	Cimetidine	Saline	
C57B110 → B10.LP	36.7 ± 14.0 (13)**	43.1 ± 7.4 (10)	0.2
B10.Br → B10.A	18.0 ± 3.3 (29)	18.0 ± 3.2 (25)	1.0
B10.D2 → B10.A	11.8 ± 1.9 (29)	12.5 ± 2.1 (25)	0.2
B10.D2 → C57B110	13.0 ± 1.9 (13)	13.5 ± 2.4 (14)	0.6
PVG/c → C57B110	7.3 ± 0.4 (15)	7.2 ± 0.6 (15)	0.7

* Student's t-test

** number of mice in parentheses

mechanisms probably play an important role (18). Moreover, skin grafting is a more sensitive method of detecting small changes in immune responsiveness (19,20).

Our investigation shows that there was no influence of cimetidine on the rejection of skin grafts in a well defined transplantation model of inbred mice, even if histoincompatibility was very weak. If there were any effect of cimetidine on graft survival this would have become apparent especially in the group with the lowest antigenic differences.

If cimetidine has an influence on cellular immune responses it is probably mediated through a blockade of suppressor T cells. Increases in delayed hypersensitivity reactions in man have been reported (4). On the other hand, it has been found that H_2-blockers sometimes inhibit delayed hypersensitivity in guinea-pigs (21). The influence of cimetidine on graft rejection in clinical renal transplantation is also controversial. Controlled clinical trials are needed before definitive conclusions can be drawn. However, on the basis of our results in an experimental model we conclude that acceleration of graft rejection by cimetidine is unlikely.

Acknowledgement

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References

1 PLAUT M, LICHTENSTEIN LM, GILLESPIE E et al: Studies on the mechanism of lymphocyte mediated cytolysis. IV Specificity of the histamine receptor on effector T-cells. J Immunol 111: 389, 1973

2 PLAUT M, LICHTENSTEIN LM, HENNEY CS: Properties of a subpopulation of T-cells bearing histamine receptors. J Clin Invest 55: 856, 1975

3 ROCKLIN RE: Modulation of cellular immune response in vivo and in vitro by histamine receptor bearing lymphocytes. J Clin Invest 57: 1051, 1976

4 AVELLA J, MADSEN JE, BINDER HJ et al: Effect of histamine H_2-receptor antagonists on delayed hypersensitivity. Lancet 1: 624, 1978

5 WANG SR, ZWEIMAN B: Histamine suppression of human lymphocyte responses to mitogen. Cell Immunol 36: 28, 1978

6 McGREGOR CGA, COCHRAN AJ, OGG LJ et al: Immunological and other laboratory studies of patients receiving short term cimetidine therapy. Lancet 1: 122, 1977

7 DE PAUW BE, LAMERS CBHW, WAGENER DJTh et al: Immunological studies after long term H_2-receptor antagonist treatment. Lancet II: 616, 1977

8 JONES RJ, RUDGE CJ, BEWICK M et al: Cimetidine: prophylaxis against upper gastrointestinal haemorrhage after renal transplantation. Brit Med J 1: 398, 1978

9 ZAMMIT M, TOLEDO-PEREYRA LH: Increased rejection after cimetidine treatment in kidney transplants. Transplantation 27: 358, 1979

10 PRIMACK WA: Cimetidine and renal allograft rejection. Lancet 1: 824, 1978

11 FESTENSTEIN H, DEMANT P: HLA and H-2. Basic Immunogenetics, biology and clinical relevance. Current Topics in Immunology Series. Arnold, London, 1978

12 GRAFF RJ, BAILEY DW: The non-H-2 histocompatibility loci and their antigens. Transplantation Rev 15: 26, 1973

13 BERDEN JHM, GERLAG PGG, HAGEMAN JFHM et al: Role of antiserum and complement in the acute antibody mediated rejection of mouse skin allografts in strain combinations with increasing histoincompatibility. Transplantation 24: 175, 1977

14 PENNYCUIK P: Unresponsiveness of nude mice to skin allografts. Transplantation 11: 417, 1971

15 RYGAARD J: Skin grafts in nude mice. Acta Pathol Microbiol Scand A 82: 80, 1974

16 GERLAG PGG, CAPEL PJA, BERDEN JHM et al: Antibody response and skin graft rejection in the nude mouse. Transplant Proc 9: 1179, 1977

17 BEVAN MJ: H_2 restriction of cytolysis after immunisation of minor H-congenic pairs of mice. Immunogenetics 3: 177, 1976

18 ISAKOV N, YANKELEVICH B, SEGAL S et al: Differential immunogenic expression of an H-2 linked histocompatibility antigen on different tissues. Differences in survival between heart, thyroid and skin allografts. Transplantation 28: 31, 1979

19 CORRY RJ, WINN HJ, RUSSELL PS: Primarily vascularized allografts of hearts in mice. Transplantation 16: 343, 1973

20 RUSSELL PS, CHASE GM, COLVIN RB et al: Kidney transplants in mice. An analysis of the immune status of mice bearing long term, H-2 incompatible transplants. J Exp Med 147: 1449, 1978

21 ASKENASE PW: Histamine-2 antagonist inhibition of delayed hypersensitivity (DH). Clin Res 25: 481, 1977

CHAPTER 9

CIMETIDINE DOES NOT INFLUENCE IMMUNOLOGICAL PARAMETERS IN MAN

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Abstract

The influence of cimetidine on several immunological parameters was studied with 3 weeks interval in 9 patients with peptic disease, before, during and 2 days after treatment with 1.6 g cimetidine daily.

No change was observed in the reaction to skin tests with candida albicans, mumps, trichophyton, intermediate strength purified protein derivative and varidase (streptokinase + streptodornase) in patients as compared to 11 controls. Neither any change occurred in total lymphocyte counts, nor in results of lymphocyte transformation tests stimulated by phytohaemagglutinin, pokeweed mitogen or a cocktail of the antigens as used for skin testing. Results of mixed lymphocyte cultures (MLC) did not alter and showed also unchanged stimulating and responding capacity of lymphocytes in one way MLC.

No difference was observed in IgG, IgA or IgM levels and all were in the normal range.

Introduction

Cimetidine is a competitive antagonist of histamine on H_2-receptors. Its main effect is a marked inhibition of gastric acid secretion and therefore it is widely used in clinical practice. As T lymphocytes bear H_2-receptors (1,2,3) concern has arisen about the possible effects of cimetidine treatment on the immune response.

Inhibition of histamine receptor bearing T cells by cimetidine might result in an enhancement of delayed type hypersensitivity reaction and some observations in vivo (4) and in vitro (5) support this hypothesis. Other studies, however, did not confirm these findings (6,7,8).

Enhancement of cellular immune response by H_2-receptor antagonists in man would be of importance since cimetidine is succesfully used in the prevention of upper gastrointestinal haemorrhage in renal transplant recipients (9). Graft rejection in renal transplantation is known to be mainly mediated by this type of reaction, and it is suggested that rejection might be increased by cimetidine (10,11). We therefore studied the influence of cimetidine on several immunological parameters in patients treated with cimetidine for peptic ulcer disease.

Patients and methods

Patients

Six males and 3 females, age ranging from 28 to 63 year, with peptic ulcer disease but otherwise healthy, entered the study after informed consent. None of the patients had been treated with cimetidine before.

Treatment

Cimetidine 400 mg four times daily was started at day 3 of the study and stopped at day 40. Patients were instructed not to take any other drug during the study. Blood cimetidine levels were assessed at day 21 and 42. This assessment was performed by high pressure liquid chromatography as described by Randolph et al (12).

Methods

The following studies were performed at day 0, 21 and 42.

- Lymphocyte count: lymphocytes were calculated from the total leucocyte and differential counts and expressed as cell number x 10^9/l. Two hundred cells were differentiated on May-Grünwald stained smears.

- Lymphocyte transformation tests: lymphocytes were cultured according to du Bois et al (13). Cell concentration was adjusted to 3 x 10^5/ml. Aliquots of 1 ml were cultured at 37°C. PHA reactivity was determined by adding 25 µg phytohaemagglutinin(Welcome MR10, Beckenham, United Kingdom) and PWM reactivity by adding 25 µg pokeweed mitogen (Gibco, New York, USA) to 1 ml lymphocyte suspension. Lymphocyte transformation by antigens was measured by means of a cocktail of antigens as described by Leguit et al (14). The cocktail contained 5 different antigens (PPD, varidase, Trichophyton antigen, candida albicans allergenic extract and mumps skin test antigen). Mixed lymphocyte cultures (MLC) were made by mixing 0.5 ml lymphocyte suspension from the patient, with 0.5 ml lymphocyte suspension from a healthy volunteer. Unilateral stimulation was measured by blocking the lymphocyte suspensions one-way by preincubation at 37°C during 30 min. with mitomycin-C (Christiaans, Brussels ,Belgium) at a final concentration of 15.4 µg/ml. The cultures with PHA were terminated on the 3rd day, all other cultures on the 6th day. To determine DNA synthesis 0.075 µCi ^{14}C-thymidine (specific activity 6.25 mCi/mmol, Amersham, United Kingdom) was added 24 hours before the cultures

were terminated. The lymphocytes were harvested on millipore microfibre glassfilters (Millipore Corp., Bedford, Mass., USA). The ^{14}C-thymidine uptake in counts per min. (CPM) was measured in a liquid scintillation counter (LKB 81000). The cultures were carried out in triplicate under sterile conditions. For each lymphocyte transformation test a healthy volunteer served as control and the same subject served as control in all successive tests in one patient. Results of tests in patients were compared with those in controls and expressed as patient to control ratio, except in mixed lymphocyte cultures, the results of which were expressed as counts per minute.

- Immunoglobulin levels: quantitative levels of IgG, IgM and IgA in serum were estimated with an automated turbidimetric immunoprecipitation method (15).

- Skin tests: skin tests were performed by intradermal injection in the forearm of 0.1 ml of: candida albicans extract 0.5:100 (Bencard, U.K.), trichophyton allergenic extract 0.5:100 (Bencard, U.K.), intermediate strength purified protein derivative (PPD, 10 1U/ml, RIV, Bilthoven, The Netherlands), mumps skin test antigen (Lilly and Co, Indianapolis, USA) and varidase (10 1U streptokinase combined with 10 1U streptodornase; Lederle Wayne, USA). Erythema and wheal size of skin tests were recorded as mm^2 at 24, 48 and 72 hours by one single observer. Maximum responses to each antigen before, during and after treatment were compared in each subject. An augmentation of 100% or more was regarded an increased reaction and a reduction of 50% or more a decreased reaction. A reaction of 20 mm^2 or more was considered to be a positive test. Negative tests which had become positive and positive tests, changed to negative, were judged as increased and decreased respectively. Results of skin tests negative on both occasions were discarded. Skin tests were also performed in a control group of 11 healthy volunteers at similar intervals.

Statistics

Results of differential counts, lymphocyte transformation tests and immunoglobulin levels were compared by Wilcoxon's rank sum test. Differences of results in skin tests in patients and controls were analysed by χ^2 analysis.

Results

Blood levels of cimetidine at day 21 were 1.30 ± 0.29 μg/ml (mean ± SE) and at day 42 nil in all patients.

The number of lymphocytes did not change and was 2.0 ± 0.2 x 10^9/l before treatment, 2.0 ± 0.2 x 10^9/l during treatment and 2.1 ± 0.1 x 10^9/l (mean ± SE) after treatment.

Results of lymphocyte transformation tests stimulated by PHA and various antigens are shown in figures 1 and 2. Although a few patients showed changes in response, reactions in most patients remained unchanged and differences in results before, during and after treatment were not significant. A similar pattern was seen in by pokeweed mitogen stimulated cultures: median patient to control ratio of counts per minute was 1.01 before, 1.02 during, and 1.11 after cimetidine treatment. Mixed lymphocyte cultures and stimulating and responding capacity of patients-lymphocytes in one way MLC did not alter significantly (figure 3).

No change was observed in IgG, IgM or IgA levels and all were within the normal range (figure 4).

The number of increased or decreased skin tests in cimetidine treated patients were not significantly different from controls. As changes in erythema did not differ from those in wheal size only the latter are represented (table 1).

Discussion

This study did not reveal any influence of treatment with cimetidine on the immunological parameters studied. Also no change was observed directly after the drug was discontinued and blood cimetidine concentrations were nil. In contrast to Avella et al (4) we did not find a more pronounced increase in skin test reactivity in patients on treatment with cimetidine compared to controls. Moreover, the results of lymphocyte cultures stimulated by a cocktail of the antigens used for skin testing, which correlate well with skin tests (14) corroborated this observation. Also 2 other T cell tests: phytohaemagglutinin stimulation and responding capacity in one way MLC did not show any change. In a previous study, in mice treated with cimetidine, we also could not demonstrate an increase of cellular immune response (8). Changes in T cell function induced by cimetidine are therefore unlikely. Likewise B lymphocyte function, as tested by pokeweed mitogen stimulation and determination of immunoglobulin levels, did not show any difference.

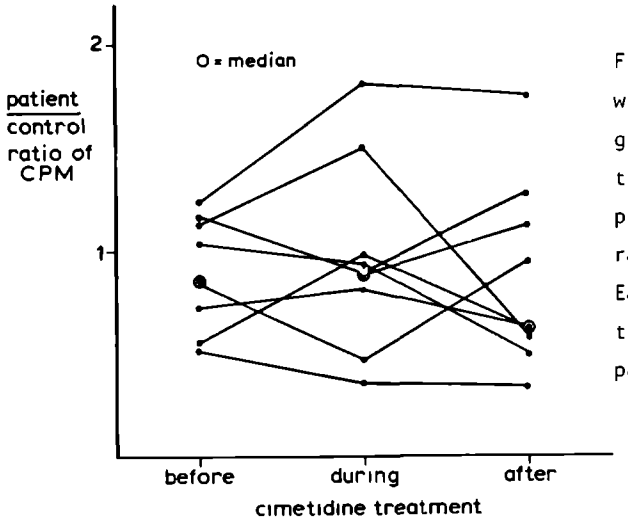

Fig 1 The effect of treatment with cimetidine on phytohaemagglutinin induced lymphocyte transformation. Data are expressed as patient to control ratio of counts per minute(CPM). Each line represents observations in one patient-control pair.

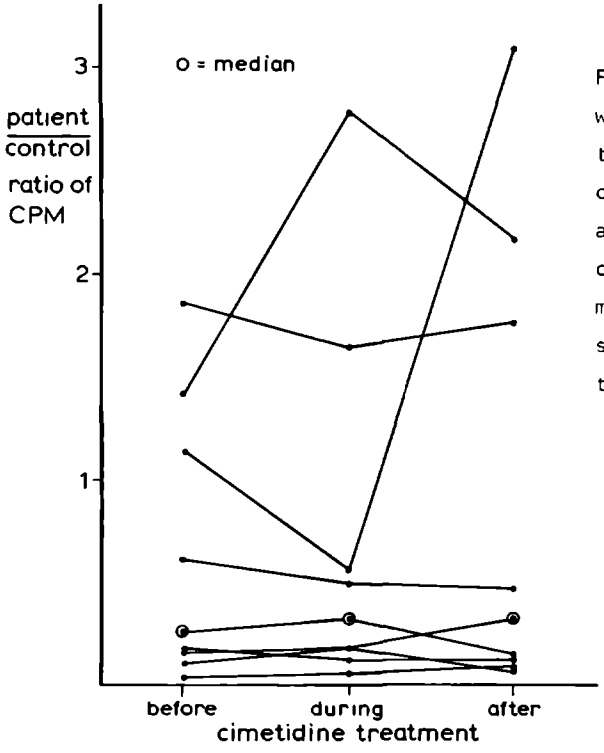

Fig 2 The effect of treatment with cimetidine on lymphocyte transformation induced by a cocktail of 5 antigens. Data are expressed as patient to control ratio of counts per minute (CPM). Each line represents observations in one patient-control pair.

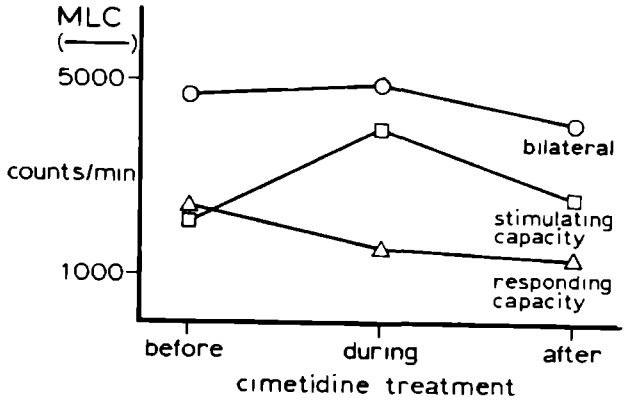

Fig 3 The effect of treatment with cimetidine on lymphocyte transformation in bilateral mixed lymphocyte cultures (MLC) and on stimulating and responding capacity in one way MLC. Data presented are the median of observations in 9 patients expressed as counts per minute.

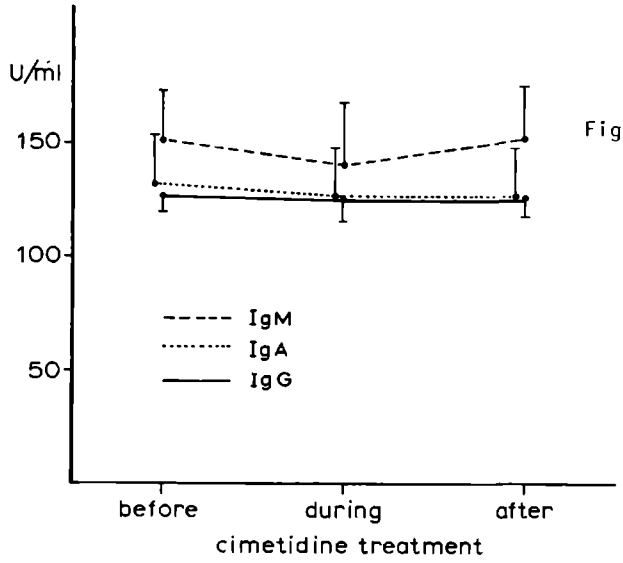

Fig 4 The effect of treatment with cimetidine on immunoglobulin levels. Data presented are the mean ± SEM of observations in 9 patients.

Table 1 EFFECT OF CIMETIDINE TREATMENT ON SKIN TESTING

Cimetidine treatment		before versus during		before versus after		during versus after	
		Cim.*	cont.**	Cim.	cont.	Cim.	cont.
mumps	: n***	9	11	9	11	9	11
	increased	3	2	1	4	1	4
	decreased	1	5	6	5	6	3
candida albicans:	n	6	3	9	6	9	6
	increased	2	3	7	6	6	5
	decreased	0	0	0	0	2	0
P.P.D.	: n	5	7	6	7	6	8
	increased	4	4	4	7	2	5
	decreased	0	0	0	0	2	1
trichophyton	: n	9	11	9	11	9	11
	increased	5	6	4	7	3	4
	decreased	1	1	1	0	3	0
varidase	: n	8	9	8	9	8	9
	increased	5	6	6	7	3	3
	decreased	0	0	1	0	1	0
total	: n	37	41	41	44	41	45
	increased	19	21	22	31	15	21
	decreased	2	6	8	5	14	4

* Cim = cimetidine treated patients; ** cont = controls; *** n = number of positive tests

If there was an effect of cimetidine on the immune response and a rebound phenomenon after stopping the drug, this would have become especially clear in comparing the results of tests during treatment to those after treatment, but no differences were demonstrated.

In conclusion, in our study no effects of short-term treatment with cimetidine on the immunological parameters studied in man were observed.

References

1 PLAUT M, LICHTENSTEIN LM, GILLESPIE E et al: Studies on the mechanism of lymphocyte mediated cytolysis. IV Specificity of the histamine receptor on effector T-cells. J Immunol 111: 389, 1973

2 PLAUT M, LICHTENSTEIN LM, HENNEY CS: Properties of a subpopulation of T-cells bearing histamine receptors. J Clin Invest 55: 856, 1975

3 ROCKLIN RE: Modulation of cellular immune response in vivo and in vitro by histamine receptor bearing lymphocytes. J Clin Invest 57: 1051, 1976

4 AVELLA J, MADSEN JE, BINDER HJ et al: Effect of histamine H_2-receptor antagonists on delayed hypersensitivity. Lancet I: 624, 1978

5 WANG SR, ZWEIMAN B: Histamine suppression of human lymphocyte responses to mitogen. Cell Immunol 36: 28, 1978

6 McGREGOR CGA, COCHRAN AJ, OGG LJ et al: Immunological and other laboratory studies of patients receiving short term cimetidine therapy. Lancet I: 122, 1977

7 DE PAUW BE, LAMERS CBHW, WAGENER DJTh et al: Immunological studies after long term H_2-receptor antagonist treatment. Lancet II: 616, 1977

8 FESTEN HPM, BERDEN JHM, KOENE RAP: Cimetidine does not accelerate skin graft rejection in mice. Clin Exp Immunol 40:193, 1980

9 JONES RH, RUDGE CJ, BEWICK M et al: Cimetidine: profylaxis against upper gastrointestinal haemorrhage after renal transplantation. Brit Med J 1: 398, 1978

10 ZAMMIT M, TOLEDO-PEREYRA LH: Increased rejection after cimetidine treatment in kidney transplants. Transplantation 27: 358, 1979

11 PRIMACK WA: Cimetidine and renal allograft rejection.Lancet I: 824, 1978

12 RANDOLPH WC, OSBORNE VL, WALKENSTEIN SS et al: High-pressure liquid chromatographic analysis of cimetidine, a histamine H_2-antagonist, in blood and urine. J Pharm Sci 66: 1148, 1977

13 DU BOIS MJGJ, HUISMANS L, SCHELLEKENS PThA et al: Investigations and standarisation of the conditions for microlymphocyte cultures. Tissue Antigen 3: 402, 1973

14 LEGUIT P Jr,MEINESZ A, HUISMANS L et al: The use of an antigen cocktail in the lymphocyte transformation test. Clin Exp Immunol 14: 149, 1973

15 VAN MUNSTER PJJ, HOELEN G: A turbidimetric immunoassay (T.I.A.) with automated individual blank compensation. Clin Chim Acta 76: 377, 1977

CHAPTER 10

CIMETIDINE IN CLINICAL USE. A REVIEW

Introduction

The classical antihistamines do not antagonize the gastric acid stimulatory effect of histamine. Ash and Schild postulated the existence of 2 different receptors for histamine (1). The effects antagonized by the classical antihistamines were defined as mediated through H_1-receptors and those who were not through H_2-receptors (1). Black and his colleagues proved this hypothesis to be true by synthesizing compounds which were able to stimulate and antagonize H_2-receptors selectively (2). Shortly afterwards H_2-receptor antagonists for clinical use were developed: metiamide, later withdrawn because of bone marrow toxicity (3) and cimetidine. At present the latter is the only commercially available H_2-receptor antagonist (Tagamet ^{R}). Pharmacological properties, results of animal studies and early clinical experiences with this drug have been reviewed (4). Since clinical experience with cimetidine in the treatment of acid-peptic diseases has rapidly increased.

The aim of this article is to review the various clinical indications for cimetidine, both proven and under investigation, and its side-effects.

Pharmacokinetics

The bioavailability of cimetidine after oral administration is about 70% (5). The blood concentration to achieve 50% inhibition of maximal gastric acid output (IC 50) is 0.5 - 1.0 µg/ml (6,7). Peak blood levels are reached 60 - 90 minutes after oral administration and the mean peak blood concentration after a 200 mg dose is 1.27 µg/ml (range 0.34 - 2.25 µg/ml). Blood levels remain above 0.5 µg/ml for more than 4 hours (6,8,9). Half-life is approximately 120 minutes. About 70% of an oral dose is excreted in the urine within 24 hours (6). However, one should bear in mind that there are great inter-individual differences in all these parameters (9,10) and that bioavailability increases with age (11,12).

Cimetidine is dosed three times 200 mg with meals and 400 mg at bedtime based on studies by Pounder and colleagues (13,14), achieving a reduction of mean 24 hour intragastric hydrogen ion concentration of 70%. Doubling of the day-time dose has no additional effect (13). Concomitant administration of anticholinergics enhances the effect of suboptimal doses of cimetidine (15,16, 17). Impaired renal function is the only condition known to require lowering of the dose (18,19).

Short term treatment

Duodenal ulcer

No drug has been so extensively studied in the treatment of duodenal ulcer as cimetidine. These studies have contributed to a better insight in this disease. For instance no endoscopically controlled data on spontaneous healing and recurrence of duodenal ulcers were known, and the results of studies with cimetidine urged to a re-evaluation of the utility of antacids in this disease (20,21).

In multiple double blind controlled trials healing rate with cimetidine after 4-6 weeks treatment was 57-84% as compared to 17-48% with a placebo (22-26). In all studies symptomatic relief in patients on cimetidine was more pronounced than with a placebo.

Gastric ulcer

The effect of cimetidine in the treatment of gastric ulcer is less clear. Some studies reported the superiority of cimetidine over a placebo in the healing of gastric ulcer, although without significant better symptomatic relief (27,28). But a number of studies fail to demonstrate a favourable effect (24,29,30). Presently it may be concluded that treatment with cimetidine is not better or worse than other medical therapies in gastric ulcer (31,32,33).

Recurrent ulcer

At present 2 controlled studies demonstrate the efficacy of cimetidine on healing and symptoms of recurrent ulcers after partial gastrectomy (34,35). A duration of therapy of 8 weeks is recommended for optimal results.

Reflux oesophagitis

Incompetence of the lower oesophageal sphincter causes reflux of gastric juice into the oesophagus. Gastric acid does not always play the key role in reflux oesophagitis since reflux of pancreatic and biliary secretions is of additional varying importance.

This complex aetiology is reflected in the equivocal results of the various clinical trials with cimetidine in reflux oesophagitis. This is not amazing as cimetidine is not known to affect other aetiological factors than gastric acid secretion. Lower oesophageal sphincter pressure is not influenced by cimetidine (36,37).

Most studies showed a favourable effect of cimetidine on heartburn symptoms (38-42), but in only some of these studies this was accompanied by a significant healing of oesophagitis (39,42). In most studies a higher dose of cimetidine was used: 4x400 mg daily during 8 weeks.

"Stress" erosion prevention

The full aetiology of stress erosion formation in poly-traumatized, extensively burned, post-operative or otherwise critically ill patients is unknown. Apart from other factors the presence of gastric acid is essential and disruption of the gastric mucosal barrier probably plays an important role (43, 44). Cimetidine inhibits gastric acid secretion and raises the gastric potential difference (45). Nevertheless, cimetidine does not affect the ionic permeability of the gastric mucosa (45) and it fails to prevent taurocholate induced disruption of the mucosal barrier (46,47). Yet, in experimental models, H_2-receptor antagonists protect against stress induced gastric mucosal injury (48-51) and they also prevent aspirin induced mucosal damage in both man (52)and rats (53). In controlled trials cimetidine prevented gastro-intestinal haemorrhage in patients with severe head injury (54), in patients with fulminant hepatic failure (55) and after renal transplantation (56). In patients with severe thermal injury cimetidine was equally effective to an intensive antacid regimen (57), but in a recent study,in critically ill patients, antacids were superior (58). This ability of antacids to protect against stress ulcer bleeding was also earlier demonstrated (59,60).Further studies on this subject will have to elucidate whether and in which conditions cimetidine is useful to prevent stress ulcer bleeding.

Gastro-intestinal haemorrhage

Controlled trials in patients with acute gastro-intestinal haemorrhage from peptic ulcer or erosions failed to demonstrate a more favourable effect of cimetidine on bleeding or re-bleeding in comparison to a placebo (61-68).

Pancreatic insufficiency

Oral pancreatic enzymes, as substitution therapy in patients with pancreatic insufficiency, are inactivated by gastric acid and pepsin. Cimetidine administered before oral pancreatic extract increases intraduodenal activity of pancreatic enzymes (69) and enhances the effectiveness of this therapy (70). In contrast to conventional high dose bicarbonate therapy cimetidine causes no discomfort.

Pancreatitis

The rationale for the use of cimetidine in acute pancreatitis is diminishing acidification of the duodenum in order to decrease the release of pancreas stimulating hormones. However, in experimental models in rats, cimetidine was eventually found to induce pancreatitis (71) and to increase the mortality rate in pancreatitis (72). In a recent clinical controlled double blind study cimetidine had neither a positive nor a negative effect on acute alcoholic pancreatitis (73).

Zollinger-Ellison syndrome

H_2-receptor antagonists have essentially changed the therapeutic approach of patients with the Zollinger-Ellison syndrome in whom radical tumor resection is impossible. Until recently the only possibility to control the symptoms of hypersecretion of gastric acid in many of these patients was total gastrectomy. Now there is ample proof that treatment with cimetidine is effective in many cases making gastric operations unnecessary (74,75,76). Most patients respond well to the drug. Often they require higher doses or addition of an anticholinergic drug (74).

Long term treatment

Duodenal ulcer

Duodenal ulcer is a chronic disease with a high relapse tendency. This prompted to study the use of cimetidine in the prevention of recurrent ulcers. There is abundant evidence that low dose cimetidine is effective in preventing relapse of duodenal ulcers (77-83). The mean remission rate after 6 to 12 months was 83% with cimetidine treatment and 25% with a placebo. There was no difference in the results if 2x400 mg cimetidine daily or only 400 mg at bedtime was used (84). Cimetidine does not cure duodenal ulcer disease. After cessation of treatment relapses in cimetidine treated patients occur as frequently as in patients on placebo (79,81,83,85). On the other hand in none of these studies the frequency of recurrence was increased after cimetidine therapy.

Gastric ulcer

The relapse rate in gastric ulcer is also high. Although the role of cimetidine in the healing of gastric ulcer is not established, 2 controlled trials studied the prevention of gastric ulcer relapse with cimetidine and the

results obtained were comparable with those in duodenal ulcer (86,87).

Recurrent ulcer

One small open trial studied the effect of long term cimetidine therapy in previously healed anastomotic ulceration. In this study 3 of 19 patients relapsed within one year treatment with 400 mg cimetidine twice daily (34).

Reflux oesophagitis

Until now no data are available on long term treatment of reflux oesophagitis with cimetidine.

Zollinger-Ellison syndrome

Long term cimetidine treatment proved to be very effective in controlling symptoms in Zollinger-Ellison patients. Many patients have been treated for much longer than one year with good result. In some instances dose adjustment was necessary but only in a few cases symptoms were uncontrolled (74,75,76).

Effects on serum gastrin and gastric acid secretion

Studies on serum gastrin after long term treatment with cimetidine show conflicting results. Some observers did not find any change at all (88). In other studies a rise of fasting serum gastrin level was seen while no change in meal stimulated gastrin occurred (89,90). Other investigators found an increase of meal stimulated gastrin only (91) and some observed a rise of both fasting and meal stimulated serum gastrin levels (92). However, since long term treatment with cimetidine in man is not found to affect gastric acid secretion (77,88,89,90,93) a possible effect on serum gastrin is not likely to be of clinical importance. On the contrary, in rats,hyperplasia and hypertrophy of parietal cells occurred after long term H_2-receptor antagonist administration, but in these studies extremely high doses were administered (94,95).

Tolerance to cimetidine does not develop during long term use: cimetidine blood levels and inhibition of gastric acid secretion remain unchanged (8,77, 90).

Side effects

Toxicology

In animal studies chronic as well as acute toxicity of cimetidine was very low (96). In man no toxicity was observed after huge overdosage of cimetidine.

In one case of self-poisoning 80 tablets of 200 mg were taken and blood cimetidine level reached 113 µg/ml without any untoward effect (97).

General side-effects

In general cimetidine is very well tolerated. The occurrence of minor side-effects is limited and necessitates withdrawal of the drug in only few instances. Minor side-effects such as headache, tiredness, diarrhoea, skin rash and muscular pain, have been observed in nearly as much patients on cimetidine as on placebo (98,99).

Kidney

A slight, often transient, rise in serum creatinine has been observed in many patients during cimetidine treatment (98,99). This rise in serum creatinine, however, is not accompanied by a decrease of creatinine clearance. Measurement of Cr^{51} EDTA and inuline clearance did neither show a decrease of renal function. It is believed therefore that the rise in serum creatinine concentration is caused by a change of the tubular handling of creatinine by the kidney (100,101).

In the United States 5 cases of interstitial nephritis, with a relapse in the single patient rechallenged, have been reported during cimetidine treatment (Smith, Kline and French, personal communication).

Liver

Slight elevations of serum transaminase levels were as frequently seen in cimetidine as in placebo treated patients. This rise is usually transitory and other biochemical liver function parameters are unaffected (98,99). Two patients on cimetidine with a rise of serum transaminase levels of clinical concern showed only "mild centrilobular necrosis" on liver biopsy (98). Recently a case of cimetidine hepatitis, probably due to a hypersensitivity type of reaction, was reported (102).

Haematological effects

Unlike metiamide cimetidine is not taken up by precursor cells in bone marrow. There are a few reports of cimetidine influencing haematological parameters. Usually these patients had complicated histories and were treated with several other drugs. Probably these reactions were idiosyncratic. Presently, it can not be concluded that cimetidine is bone-marrow toxic. This subject has recently been reviewed (103).

Endocrine effects

Hall was the first to report gynaecomastia in patients during cimetidine treatment (104) and consequently several other cases have been reported. In these patients no hormonal dysfunction was detected (104,105). Several studies report a rapid and brief stimulation of prolactin release after intravenous bolus injection of cimetidine, but not after oral cimetidine (106,107,108). In one study an influence on the hypothalamic-pituitary-testicular axis was seen with a decrease of sperm counts,within normal limits, in 7 patients after 9 weeks cimetidine therapy (109). In rats the existence of a certain anti-androgenic effect of cimetidine is supported by several observations. The size of prostates and seminal vesicles decreased after one month high dose cimetidine administration (96,110), and in in vitro experiments cimetidine occupied androgen receptors (110,111). Most studies in man, however, did not disclose an effect on pituitary or testicular hormones after treatment with cimetidine for up to 3 months (107, 112, 113). In controlled trials on short term and maintenance treatment with cimetidine no sexual dysfunction was spontaneously reported by the patients. Such an effect however, may solely be detected after explicit inquiry.

In conclusion, certain endocrine effects of cimetidine are probably present but future studies will have to determine whether these effects are of clinical importance. Currently, attention and caution are recommended especially during long term treatment with cimetidine.

CNS-effects

In several mostly older and severely ill patients with decreased renal and hepatic function cimetidine-induced mental confusion is reported (114, 115). These symptoms subside rapidly after discontinuation of the drug. In these patients higher blood cimetidine levels are reached and the blood-brain barrier is permeable to cimetidine (114). Adaptation of the dose under careful observation is recommended under these circumstances.

Interactions with other drugs

Cimetidine enhances the effect of oral anticoagulants probably by interfering with the metabolism of warfarin (116,117). Another study showed comparable interference with the metabolism of diazepam by cimetidine (118). These interactions may be due to inhibition of the microsomal drug metabolism in the liver by cimetidine as observed in the rat (119). For this reason cimetidine might interact with the hepatic metabolism of other drugs and

therefore further studies in this field are indicated.

Immunological effects

A subpopulation of T lymphocytes is known to have H_2-receptors (120) and therefore concern has arisen about a possible enhancement of delayed type hypersensitivity by cimetidine which might cause an increase in renal allograft rejection (121). Indeed, one study in man showed increased reaction to skin tests for delayed type hypersensitivity (122) and in another study an increased rejection of renal allografts was observed in dogs treated with cimetidine (123). But the first study (122) had a disputable design (124) and we have not been able to reproduce its results (125). In a well defined transplantation model of inbred mice cimetidine did not increase skin graft rejection even if antigenic disparity was very weak (126). There are several other investigations which do not support a clinical important change in the immune response induced by cimetidine (125,127,128). In one study in renal transplant recipients no increase of graft rejection was observed during cimetidine therapy (129).

Although there may be a certain immunological effect of cimetidine, up till now its clinical relevance is not established.

Response of malignant ulcers

In patients with a malignant gastric ulcer cimetidine may achieve a misleading favourable response thus masking the diagnosis (130).

Carcinogenic effects

Concern has been raised because cimetidine might form nitroso metabolites which might be involved in the pathogenesis of gastric cancer (131,132). Up till the time of writing there is no indication neither clinical nor experimental that supports this hypothesis (133,134,135).

Effect on cardiac histamine receptors

Histamine H_2-receptors have been demonstrated in the heart (136). There are a few case-reports in which arrythmias were attributed to cimetidine treatment (137,138). In 2 studies on this subject, however, no effect of cimetidine on heart rate could be established (139,140).

Conclusion

Cimetidine has proven to be a useful drug. It is clearly beneficial in the treatment of duodenal ulcer, recurrent ulcers after gastric surgery and

the Zollinger-Ellison syndrome. In view of uncertainty of long term side-effects its use for maintenance treatment is recommended in selected patients only. Its role in the treatment of gastric ulcer and reflux oesophagitis is less clear. More data are required on stress ulcer prevention by cimetidine. Side-effects are relatively rare and benign: presently the occurrence of endocrine effects and interactions with other drugs primarily cause anxiety, but full clinical importance has not yet been established. Short term treatment seems safe.

References

1 ASH ASF, SCHILD HO: Receptors mediating some actions of histamine. Br J Pharmac Chemother 27: 427, 1966

2 BLACK JW, DUNCAN WAM, DURANT CJ et al: Definition and antagonism of histamine H_2-receptors. Nature 236: 385, 1972

3 FORREST JAH, SHEARMAN DJC, SPENCE R et al: Neutropenia associated with metiamide. Lancet 1: 392, 1975

4 BROGDEN RN,HEEL RC, SPEIGHT TM et al: Cimetidine: a review of its pharmacological properties and therapeutic efficacy in peptic ulcer disease. Drugs 15: 93, 1978

5 GRIFFITHS R, LEE RM, TAYLOR DC: Kinetics of cimetidine in man and experimental animals. In: Cimetidine: Proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland and MA Simkins. Amsterdam-Oxford, Excerpta Medica, 1977, p 38

6 BURLAND WL, DUNCAN WAM, HESSELBO T et al: Pharmacological evaluation of cimetidine, a new histamine H_2-receptor antagonist, in healthy man. Br J Clin Pharmac 2: 481, 1975

7 BODEMAR G, NORLANDER B, WALAN A: Cimetidine in the treatment of active peptic ulcer disease. In: Cimetidine: Proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland and MA Simkins. Amsterdam-Oxford, Excerpta Medica, 1977, p 224

8 BODEMAR G, NORLANDER B, FRANSSON L et al: The absorption of cimetidine before and during maintenance treatment with cimetidine and the influence of a meal on the absorption of cimetidine. Studies in patients with peptic ulcer disease. Br J Clin Pharmac 7: 23, 1979

9 RUNE SJ, HESSELFELDT P, LARSEN NE: Clinical and pharmacological effectiveness of cimetidine in duodenal ulcer patients. Scand J Gastroent 14: 489, 1979

10 GRAHNEN A, VON BAHR C, LINDSTRÖM B et al: Bioavailability and pharmacokinetics of cimetidine. Eur J Clin Pharmacol 16: 335, 1979

11 REDOLFI A, BORGOGELLI E, LODOLA E: Blood levels of cimetidine in relation to age. Eur J Clin Pharmacol 15: 257, 1979

12 SOMOGYI A, ROHNER HG, GUGLER R: Pharmacokinetics and bioavailability of cimetidine in gastric and duodenal ulcer patients. Clin Pharmacokinetics 5: 84, 1980

13 POUNDER RE, WILLIAMS JG, MILTON-THOMPSON GJ et al: 24-Hour control of intragastric acidity by cimetidine in duodenal ulcer patients.Lancet 2: 1069, 1975

14 POUNDER RE, WILLIAMS JG, MILTON-THOMPSON GJ et al: Effect of cimetidine on 24-hour intragastric acidity in normal subjects. Gut 17: 133, 1976

15 POUNDER RE, HUNT RH, VINCENT SH et al: 24-Hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer during oral administration of cimetidine and atropine. Gut 18: 85, 1977

16 BLACKWOOD WS, NORTHFIELD TC: Nocturnal gastric acid secretion: effect of cimetidine and interaction with anticholinergics. In: Cimetidine:Proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland and MA Simkins. Amsterdam-Oxford, Excerpta Medica, 1977, p 124

17 FELDMAN M, RICHARDSON CT, PETERSON WL et al: Effect of low-dose propantheline on food stimulated acid secretion. N Engl J Med 297: 1427,1977

18 CANAVAN JSF, BRIGGS JD: Cimetidine clearance in renal failure. In: Cimetidine: Proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland and MA Simkins. Amsterdam-Oxford, Excerpta Medica, 1977, p 75

19 LARSSON R, BODEMAR G, NORLANDER B:Oral absorption of cimetidine and its clearance in patients with renal failure.Eur J Clin Pharmacol 15:153,1979

20 PETERSON WL, STURDEVANT RAL, FRANKL HD et al: Healing of duodenal ulcer with an antacid regimen. N Engl J Med 297: 341, 1977

21 IPPOLITI AF, STURDEVANT RAL, ISENBERG JI et al: Cimetidine versus intensive antacid therapy for duodenal ulcer. A multicenter trial. Gastroenterology 74: 393, 1978

22 BODEMAR G, WALAN A: Cimetidine in the treatment of active duodenal and prepyloric ulcers. Lancet 2: 161, 1976

23 BLACKWOOD WS, MAUDGAL DP, PICKARD RG et al: Cimetidine in duodenal ulcer. Lancet 2: 174, 1976

24 FESTEN HPM, LAMERS CBH, VAN TONGEREN JHM: De onderdrukking van de maagzuurproductie door middel van cimetidine: resultaten van een dubbelblind onderzoek naar de betekenis van cimetidine voor de behandeling van peptische ulcera. Ned T Geneesk 122: 862, 1978

25 BINDER HJ, COCCO A, CROSSLEY RJ et al: Cimetidine in the treatment of duodenal ulcer. A multicenter double blind study. Gastroenterology 74: 380, 1978

26 HETZEL DJ, HANSKY J, SHEARMAN DJC et al: Cimetidine treatment of duodenal ulceration. Short term clinical trial and maintenance study. Gastroenterology 74: 389, 1978

27 FROST F, RAHBEK I, RUNE SJ et al: Cimetidine in patients with gastric ulcer: a multicenter controlled trial. Br Med J 2: 795, 1977

28 BADER JP, MORIN T, BERNIER JJ et al: Treatment of gastric ulcer by cimetidine. A multicenter trial. In: Cimetidine: Proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland and MA Simkins. Amsterdam-Oxford, Excerpta Medica, 1977 p 287

29 DYCK WP, BELSITO A, FLESHLER B et al: Cimetidine and placebo in the treatment of benign gastric ulcer. A multicenter double blind study. Gastroenterology 74: 410, 1978

30 CICLITIRA PH, MACHELL RJ, FARTHING MJG et al: Double blind controlled trial of cimetidine in the healing of gastric ulcer. Gut 20: 730, 1979

31 ENGLERT E Jr,FRESTON JW, GRAHAM DY et al: Cimetidine, antacid and hospitalization in the treatment of benign gastric ulcer. A multicenter double blind study. Gastroenterology 74: 416, 1978

32 MORGAN AG, McADAM WAF, PACSOO C et al: Cimetidine: an advance in gastric ulcer treatment? Br Med J 2: 1323, 1978

33 LA BROOY SJ,TAYLOR RH, HUNT RJ et al: Controlled comparison of cimetidine and carbenoxolone sodium in gastric ulcer. Br Med J 1: 1308, 1979

34 FESTEN HPM, LAMERS CBH, DRIESSEN WMM et al: Cimetidine in anastomotic ulceration after partial gastrectomy. Gastroenterology 76: 83, 1979

35 GUGLER R, LINDSTAEDT H, MIEDERER S et al: Cimetidine for anastomotic ulcers after partial gastrectomy. N Engl J Med 301: 1077, 1979

36 FREELAND GR, HIGGS RH, CASTELL DO: Lower esophageal sphincter response to oral administration of cimetidine in normal subjects. Gastroenterology 72: 28, 1977

37 OSBORNE DH, LENNON J, HENDERSON M et al: Effect of cimetidine on the human lower oesophageal sphincter. Gut 18: 99, 1977

38 BEHAR J, BRAND DL, BROWN FC et al: Cimetidine in the treatment of symptomatic gastroesophageal reflux. A double blind controlled trial. Gastroenterology 74: 441, 1978

39 WESDORP E, BARTELSMAN J, PAPE K et al: Oral cimetidine in reflux esophagitis: a double blind controlled trial. Gastroenterology 79: 821, 1978

40 POWELL-JACKSON PR, BARKLEY H, NORTHFIELD TC: Effect of cimetidine in symptomatic gastro-oesophageal reflux. Lancet 2: 1068, 1978

41 FERGUSON R, DRONFIELD MW, ATKINSON M: Cimetidine in the treatment of reflux oesophagitis with peptic stricture. Br MEd J 2: 472, 1979

42 LEPSIEN G, SONNENBERG A, BERGES W et al: Die Behandlung der Refluxösophagitis mit cimetidin. Dtsch Med Wschr 104: 901, 1979

43 DAVENPORT HW: Back diffusion of acid through the gastric mucosa and its physiological consequences. In: Progress in gastroenterology. Vol 2, edited by J Glass, Grune and Stratton, New York 1970, p 42

44 SKILLMAN JJ, GOULD SA, CHUNG RSK et al: The gastric mucosal barrier: Clinical and experimental studies in critically ill and normal man, and in the rabbit. Ann Surg 172: 564, 1970

45 IVEY KJ, MACKERCHER PA: Effect of cimetidine on ion fluxes and potential difference across the human stomach. Gut 19: 414, 1978

46 REES WDW, RHODES J, WHEELER MH et al: The role of histamine receptors in the pathophysiology of gastric mucosal damage. Gastroenterology 72: 67, 1977

47 KENYON GS, ANSELL IF, CARTER DC: Cimetidine and the gastric mucosal barrier. Gut 18: 631, 1977

48 SAFAIE-SHIRAZI S, FOSTER LD, HARDY BM: The effect of metiamide, an H_2-receptor antagonist, in the prevention of experimental stress ulcers. Gastroenterology 71: 421, 1976

49 STRAUSS RJ, STEIN TA, WISE L: Prevention of stress ulcerations using H_2-receptor antagonists. Am J Surg 135: 120, 1978

50 LEVINE BA, SIRINEK KR, PRUITT BA Jr: Cimetidine protects against stress induced gastric injury by mucosal barrier breakers. Am J Surg 137: 328, 1979

51 LEVINE BA, SIRINEK KR, McLEOD CG et al: The role of cimetidine in the prevention of stress induced gastric mucosal injury. Surg Gynec Obstet 148: 399, 1979

52 WELCH RW, BENTCH HL, HARRIS SC: Reduction of aspirin induced gastrointestinal bleeding with cimetidine. Gastroenterology 74: 459, 1978

53 GUTH PH, AURES D, PAULSEN G: Topical aspirin plus HCL gastric lesions in the rat. Gastroenterology 76: 88, 1979

54 HALLORAN LG, ZFASS AM, GAYLE WE et al: Prevention of acute gastrointestinal complications after severe head injury: a controlled trial of cimetidine prophylaxis. Am J Surg 139: 44, 1980

55 MACDOUGALL BRD, BAILEY RJ, WILLIAMS R: H_2-receptor antagonists and antacids in the prevention of acute gastrointestinal haemorrhage in fulminant hepatic failure. Lancet 1: 617, 1977

56 JONES RH, RUDGE CJ, BEWICK M et al: Cimetidine: prophylaxis against upper gastrointestinal haemorrhage after renal transplantation. Br Med J 1: 398, 1978

57 McELWEE HP, SIRINEK KR, LEVINE BA: Cimetidine affords protection equal to antacids in prevention of stress ulceration following thermal injury. Surgery 86: 620, 1979

58 PRIEBE HJ, SKILLMAN JJ, BUSHNELL LS et al: Antacids versus cimetidine in preventing acute gastrointestinal bleeding. N Engl J Med 302: 426, 1980

59 McALHANY JC Jr, CZAJA AJ, PRUITT BA Jr: Antacid control of complications from acute gastroduodenal disease after burns. J Trauma 16: 645, 1976

60 HASTINGS PR, SKILLMAN JJ, BUSHNELL LS et al: Antacid prophylaxis of bleeding in the critically ill. N Engl J Med 298: 1041, 1978

61 EDEN K, KERN F Jr: Current status of cimetidine in upper gastrointestinal bleeding. Gastroenterology 74: 466, 1978

62 GALMICHE JP, COLIN R, HECKETSWEILER P et al: Traitement des hémorragies digestives ulcéreuses par la cimetidine. Gastroenterol Clin Biol 2: 771, 1978

63 PICKARD RG, SANDERSON I, SOUTH M et al: Controlled trial of cimetidine in acute upper gastrointestinal bleeding. Br Med J 1: 661, 1979

64 SIDDIQI SMZA, TILDESLEY G, PICKENS PT et al: Cimetidine in acute gastrointestinal bleeding. Br Med J 1: 954, 1979

65 LaBROOY SJ, MISIEWICZ JJ, EDWARDS J et al: Controlled trial of cimetidine in upper gastrointestinal haemorrhage. Gut 20: 892, 1979

66 HOARE AM, BRADBY GVH, HAWKINS CF et al: Cimetidine in bleeding peptic ulcer. Lancet 2: 671, 1979

67 MACKLON AF, ROBERTS SH, JAMES O: Cimetidine in bleeding peptic ulcer. Lancet 2: 1135, 1979

68 CARSTENSEN HE, BÜLOW S, HART HANSEN O et al: Cimetidine for severe gastroduodenal haemorrhage: a randomized controlled trial. Scand J Gastroent 15: 103, 1980

69 SAUNDERS JHB, DRUMMOND S, WORMSLEY KG: Inhibition of gastric secretion in treatment of pancreatic insufficiency. Br Med J 1: 418, 1977

70 REGAN PT, MALAGELADA JR, DiMAGNO EP et al: Comparative effects of antacids, cimetidine and enteric coating on the therapeutic response to oral enzymes in severe pancreatic insufficiency. N Engl J Med 297: 854, 1977

71 JOFFE SN, LEE FD: Acute pancreatitis after cimetidine administration in experimental duodenal ulcer. Lancet 1: 383, 1978

72 HADAS N, WAPNICK S, GROSKERO SJ: Cimetidine in pancreatitis. N Engl J Med 299: 487, 1978

73 MESHKINPOUR H, MOLINARI MD, GARDNER L et al: Cimetidine in the treatment of acute alcoholic pancreatitis. Gastroenterology 77: 687, 1979

74 McCARTHY DM: Report on the United States experience with cimetidine in Zollinger-Ellison syndrome and other hypersecretory states. Gastroenterology 74: 453, 1978

75 LAMERS CBH, FESTEN HPM, VAN TONGEREN JHM: Long-term treatment with histamine H_2-receptor antagonists in Zollinger-Ellison syndrome. Am J Gastroenterol 70: 286, 1978

76 STAGE JG, STADIL F, FISCHERMAN K: New aspects in the treatment of the Zollinger-Ellison syndrome. In:Cimetidine, proceedings of an international symposium on histamine H_2-receptor antagonists. Edited by W Creutzfeldt. Amsterdam-Oxford, Excerpta Medica, 1978, p 137

77 BODEMAR G, WALAN A: Maintenance treatment of recurrent peptic ulcer by cimetidine. Lancet 1: 403, 1978

78 BLACKWOOD WS, MAUDGAL DP, NORTHFIELD TC: Prevention by bedtime cimetidine of duodenal ulcer relapse. Lancet 1: 626, 1978

79 GUDMAND-HØYER E, BIRGER JENSEN K, KRAG E et al: Prophylactic effect of cimetidine in duodenal ulcer disease. Br Med J 1: 1095, 1978

80 BARDHAN KD, SAUL DM, EDWARDS JL et al: Double-blind comparison of cimetidine and placebo in the maintenance of healing of chronic duodenal ulceration. Gut 20: 158, 1979

81 DRONFIELD MW, BATCHELOR AJ, LARKWORTHY W et al: Controlled trial of maintenance cimetidine treatment in healed duodenal ulcer: short and long term effects. Gut 20: 526, 1979

82 BERSTAD A, AADLAND E, CARLSEN E et al: Maintenance treatment of duodenal ulcer patients with a single bedtime dose of cimetidine. Scand J Gastroent 14: 827, 1979

83 SALERA M, TARONI F, MIGLIOLI M et al: Long term effects and after effects of cimetidine in duodenal ulcer patients. Ital J Gastroenterol 11:49,1979

84 BURLAND WL, HAWKINS BW, HORTON RJ et al: The longer term treatment of duodenal ulcer with cimetidine. In: Cimetidine, proceedings of the Westminster Hospital symposium 1978. Edited by C Wastell and P Lance. Edinburgh-London and New York, Churchill Livingstone, 1978, p 66

85 CARGILL JM, PEDEN N, SAUNDERS JHB et al: Very long term treatment of peptic ulcer with cimetidine. Lancet 2: 1113, 1978

86 BIRGER JENSEN K, MØLMANN KM, RAHBEK I et al: Prophylactic effect of cimetidine in gastric ulcer patients. Scand J Gastroent 14: 175, 1979

87 MACHELL RJ, CICLITIRA PJ, FARTHING MJG et al: Cimetidine in the prevention of gastric ulcer relapse. Postgraduate Medical Journal 55: 393, 1979

88 ARNOLD R, CREUTZFELDT W: Basal and meal stimulated serum gastrin, antral G-cells and gastrin concentration during cimetidine therapy. In: Cimetidine, proceedings of an international symposium on histamine H_2-receptor antagonists.Edited by W Creutzfeldt.Amsterdam-Oxford,Excerpta Medica,1978,p 87

89 FORREST JAH, FETTES MR, Mc LOUGHLIN GP et al: Effect of long term cimetidine on gastric acid secretion, serum gastrin, and gastric emptying. Gut 20: 404, 1979

90 FESTEN H, LAMERS C, TANGERMAN A et al: Effect of one year treatment with cimetidine on gastric acid secretion, serum gastrin, blood concentration of cimetidine, and inhibition of gastric acid secretion by cimetidine in duodenal and gastric ulcer patients Gut 20: A 451, 1979

91 SEWING KF, HAGIE L, IPPOLITI AF et al: Effect of one month treatment with cimetidine on gastric secretion and serum gastrin and pepsinogen levels. Gastroenterology 74: 376, 1978

92 SPENCE RW, Mc CORMICK DA, OLIVER JM et al: The effect on serum gastrin of withdrawal of cimetidine after one year's treatment.In:Cimetidine, proceedings of the Westminster Hospital symposium 1978. Edited by C Wastell and P Lance. Edinburgh-London and New York, Churchill Livingstone, 1978, p 153

93 SPENCE RW, CELESTIN LR, Mc CORMICK DA et al: The effect of long term treatment with cimetidine on gastric acid secretion and gastric responses in man. In: Cimetidine, proceedings of an international symposium on histamine H_2-receptor antagonists. Edited by W Creutzfeldt. Amsterdam-Oxford, Excerpta Medica, 1978, p 116

94 WITZEL L, HALTER F, OLAH AJ et al: Effects of prolonged metiamide medication on the fundic mucosa. Gastroenterology 73: 797, 1977

95 CREAN GP, DANIEL D, LESLIE GB et al: The effects of prolonged administration of large doses of cimetidine on the gastric mucosa of rats. In: Cimetidine, proceedings of the Westminster Hospital symposium 1978. Edited by C Wastell and P Lance. Edinburgh-London and New York, Churchill Livingstone 1978, p 191

96 LESLIE GB, WALKER TF: A toxicological profile of cimetidine. In: Cimetidine: Proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland and MA Simkins. Amsterdam-Oxford, Excerpta Medica 1977, p 24

97 ILLINGWORTH RN, JARVIE DR: Absence of toxicity in cimetidine overdosage. Br Med J 1: 453, 1979

98 SHARPE PC, HAWKINS BW: Efficacy and safety of cimetidine. Long term treatment with cimetidine. In: Cimetidine: Proceedings of the second international symposium on histamine H_2-receptor antagonists. Edited by WL Burland and MA Simkins. Amsterdam-Oxford, Excerpta Medica 1977, p 358

99 KRUSS DM, LITTMAN A: Safety of cimetidine. Gastroenterology 74: 478, 1978

100 DUBB JW, STOTE RM, FAMILIAR RG et al: Effect of cimetidine on renal function in normal man. Clin Pharmacol Ther 24: 76, 1978

101 LARSSON R, BODEMAR G, KAGEDAL B: The effect of cimetidine, a new histamine H_2-receptor antagonist, on renal function. Acta Med Scand 205: 87, 1979

102 VILLENEUVE JP,WARNER HA: Cimetidine hepatitis. Gastroenterology 77: 143, 1979

103 FRESTON JW: Cimetidine and granulocytopenia. Ann Intern Med 90: 264,1979

104 HALL WH: Breast changes in males on cimetidine. N Engl J Med 295: 841, 1976

105 SPENCE RW, CELESTIN LR: Gynaecomastia associated with cimetidine. Gut 20: 154, 1979

106 CARLSON HE, IPPOLITI AF: Cimetidine, an H_2-antihistamine, stimulates prolactin secretion in man. J Clin Endocrinol Metab 45: 367, 1977

107 DAUBRESSE JC, MEUNIER JC, LIGNY G: Effects of acute and chronic cimetidine administration on the pituitary testicular axis. Agressologie 20: 71, 1979

108 BURLAND WL, GLEADLE RI, LEE RM et al: Prolactin responses to cimetidine. Br J Clin Pharmac 7: 19, 1979

109 VAN THIEL DM, GAVALER JS, SMITH WI et al:Hypothalamic-pituitary-gonodal dysfunction in men using cimetidine. N Engl J Med 300: 1012, 1979

110 WINTERS SJ, BANKS JL, LORIAUX DL: Cimetidine is an antiandrogen in the rat. Gastroenterology 76: 504, 1979

111 FUNDER JW, MERCER JE: Cimetidine, a histamine H_2-receptor antagonist, occupies androgen receptors. J Clin Endocrinol Metab 48: 189, 1979

112 BARBER SG, HOARE AM: Cimetidine effects on prolactin release and production. Horm Metab Res 11: 220, 1979

113 WHITE MC, GORE M, JEWELL DP: Endocrine function after cimetidine. N Engl J Med 301: 503, 1979

114 SCHENTAG JJ, CERRA FB, CALLERI G et al: Pharmacokinetic and clinical studies in patients with cimetidine-associated mental confusion. Lancet 1: 177 , 1979

115 MOGELNICKI SR, WALLER JL, FINLAYSON DC: Physostigmine reversal of cimetidine-induced mental confusion. JAMA 241: 826, 1979

116 SERLIN MJ, SIBEON RG, MOSSMAN S et al: Cimetidine: interaction with oral anticoagulants in man. Lancet 2: 317, 1979

117 SILVER BA, BELL WR: Cimetidine potentiation of the hypoprothrombinemic effect of warfarin. Ann Intern Med 89: 348, 1979

118 KLOTZ U, ANTILLA VJ, REIMANN I: Cimetidine/Diazepam interaction. Lancet 2: 699, 1979

119 PUURUMEN J, PELKONEN O: Cimetidine inhibits microsomal drug metabolism in the rat. Eur J Pharmacol 55: 335, 1979

120 PLAUT M, LICHTENSTEIN LM, HENNEY CS: Properties of a subpopulation of T-cells bearing histamine receptors. J Clin Invest 55: 856, 1975

121 PRIMACK WA: Cimetidine and renal-allograft rejection. Lancet 1: 824, 1978

122 AVELLA J, MADSEN JE, BINDER HJ et al: Effect of histamine H_2-receptor antagonists on delayed hypersensitivity. Lancet 1: 624, 1978

123 ZAMMIT M, TOLEDO-PEREYRA LH: Cimetidine for kidney transplantation: experimental observations. Surgery 86: 611, 1979

124 GOODWIN JS: Cimetidine and delayed hypersensitivity. Lancet 1: 934, 1978

125 FESTEN HPM, BERDEN JHM, DE PAUW BE: Immunological studies in patients treated with cimetidine and the influence of cimetidine on skin-graft survival in mice. In: Proceedings of a European symposiun on further experience with H_2-receptor antagonists in peptic ulcer disease and progress in histamine research. Capri 1979. Edited by A Torsoli and P Lucchelli. Amsterdam-Oxford-Princeton, Excerpta Medica 1980 (in press)

126 FESTEN HPM, BERDEN JHM, KOENE RAP: Cimetidine does not accelerate skin graft rejection in mice. Clin Exp Immunol 40: 193, 1980

127 Mc GREGOR CGA, COCHRAN AJ, OGG LJ et al: Immunological and other laboratory studies of patients receiving short term cimetidine therapy. Lancet 1: 122, 1977

128 DE PAUW BE, LAMERS CBHW, WAGENER DJTh et al: Immunological studies after long term H_2-receptor-antagonist therapy. Lancet 2: 616, 1977

129 VANRENTERGHEM Y, ROELS L, MICHIELSEN P: Prophylactic treatment with cimetidine after renal transplantation. In: Proceedings of a European symposium on further experience with H_2-receptor antagonists in peptic ulcer disease and progress in histamine research. Capri 1979. Edited by A Torsoli and P Lucchelli. Amsterdam-Oxford-Princeton, Excerpta Medica 1980 (in press)

130 TAYLOR RH, MENZIES-GOW N, LOVELL D et al: Misleading response of malignant gastric ulcers to cimetidine. Lancet 1: 686, 1978

131 ELDER JB, GANGULI PC, GILLESPIE IE: Cimetidine and gastric cancer. Lancet 1: 1005, 1979

132 ELDER JB, GANGULI PC, GILLESPIE IE: Gastric cancer in patients who have taken cimetidine. Lancet 2: 245, 1979

133 ROE FJC: Cimetidine and gastric cancer. Lancet 1: 1039, 1979

134 RUDDELL WSJ: Gastric cancer in patients who have taken cimetidine. Lancet 1: 1234, 1979

135 CREAN GP, LESLIE GB, ROE FJC: Cimetidine and gastric cancer: negative studies in dogs. Lancet 2: 797, 1979

136 LEVI R, CAPURRO N, LEE CH: Pharmacological characterization of cardiac histamine receptors: sensitivity to H_1- and H_2-receptor agonists and antagonists. European J Pharmacol 30: 328, 1975

137 JEFFERYS DB, VALE JA: Cimetidine and bradycardia. Lancet 1: 828, 1978

138 COHEN J, WEETMAN AP, DARGIE HJ et al: Life-threatening arrhythmias and intravenous cimetidine. Br Med J 2: 768, 1979

139 ENGEL TR, LUCK JC: Histamine-2-receptor antagonism by cimetidine and sinus-node function. N Engl J Med 301: 591, 1979

140 SAMUEL IO, DUNDEE JW: Influence of cimetidine on cardiovascular parameters in man. J Royal Soc Med 72: 898, 1979

Hoofdstuk 1: Inleiding en opzet van het onderzoek

Maagzuur speelt een grote rol bij de pathogenese van het ulcus pepticum. De parietale cel in de maagwand produceert het maagzuur en wordt hiertoe aangezet door acetylcholine, gastrine en histamine. Voor histamine zijn in de weefsels 2 verschillende receptoren aanwezig: de H_1-receptoren via welke voornamelijk de contractie van glad spierweefsel in bronchi, ileum en arteriën wordt bewerkstelligd en de H_2-receptoren via welke als voornaamste effect de maagzuurproductie wordt gestimuleerd.

Cimetidine is een stof die in staat is het effect van histamine op de H_2-receptoren competitief te antagoneren. Zodoende wordt door cimetidine de maagzuurproductie sterk geremd. Daarom wordt dit geneesmiddel toegepast bij die ziekten waarbij van de vermindering van het maagzuur een gunstig effect wordt verwacht. De onderzoeken die in het kader van deze studie met cimetidine werden verricht worden in dit hoofdstuk beschreven.

Hoofdstuk 2: De onderdrukking van de maagzuurproductie door middel van cimetidine en de resultaten van een dubbelblind onderzoek naar de betekenis van cimetidine voor de behandeling van peptische ulcera.

Een daling van zowel de basale als de met pentagastrine gestimuleerde maagzuurproductie is vastgesteld na orale toediening van 200 mg cimetidine aan 14 patienten met een ulcus duodeni en 8 met een ulcus ventriculi.

In een dubbelblind onderzoek werd het effect van cimetidine op de ulcusgenezing vergeleken met dat van een placebo. Van 23 patienten met een ulcus duodeni waren na 4 weken 10 van de 12 patienten behandeld met cimetidine en 2 van de 11 patienten behandeld met een placebo genezen ($p<0,01$). Bij de met cimetidine behandelde patienten waren ook de klachten significant verminderd.

Bij 9 van de 13 patienten met een ulcus ventriculi was het ulcus genezen na 4 weken behandeling met cimetidine en bij 4 van de 11 die een placebobehandeling kregen (niet significant). Zowel bij de met cimetidine als bij de met placebo behandelde patienten verminderden de klachten significant.

Als bijwerking werd bij enkele patienten, zowel in de cimetidinegroep als in mindere mate ook in de placebogroep, een geringe voorbijgaande stijging gezien van het gehalte aan kreatinine en SGPT in het serum.

Geconcludeerd wordt dat cimetidine de maagzuurproductie effectief remt bij zowel ulcus duodeni als ulcus ventriculi patienten. Patienten met een

ulcus duodeni reageren ook gunstig op de behandeling met cimetidine. Bij patienten met een ulcus ventriculi is het nut van behandeling met cimetidine minder duidelijk.

Hoofdstuk 3: De behandeling van het anastomose ulcus na maagresectie met cimetidine

Eenentwintig patienten met een anastomose ulcus na een maagresectie namen deel aan een dubbelblind onderzoek om het effect van cimetidine op de ulcusgenezing te vergelijken met dat van een placebo. Bij gastroscopie na 4 weken behandeling bleken 8 van de 12 met cimetidine behandelde patienten te zijn genezen en één van de 9 die een placebo kregen ($p<0,05$). De behandeling met cimetidine had ook een gunstiger effect op de klachten van de patienten dan placebobehandeling. Na één maand cimetidinebehandeling genas 67% van de patienten en na 2 maanden behandeling 86%.

Gedurende 1 jaar onderhoudsbehandeling met 2x400 mg cimetidine per dag kregen 3 van de 19 behandelde patienten een recidief ulcus.

Tijdens de behandeling werden geen bijwerkingen van betekenis geconstateerd.

Geconcludeerd wordt dat het stoma ulcus na een maagresectie goed reageert op de behandeling met cimetidine; in een aantal gevallen zal echter een langere behandelingsduur dan 4 weken nodig zijn.

Hoofdstuk 4: De behandeling van ernstige ulcererende reflux oesofagitis met cimetidine; de resultaten van een dubbelblind onderzoek gedurende 8 weken en van een daaropvolgende onderhoudsbehandeling.

Bij 20 patienten met een door middel van oesofagoscopie aangetoonde ernstige ulcererende reflux oesofagitis werd in een dubbelblind onderzoek het effect van de behandeling met 1,6 g cimetidine per dag vergeleken met dan van placebobehandeling.

Na 8 weken was de oesofagitis bij 6 van de 13 met cimetidine behandelde patienten genezen en bij één van de 7 die met placebo werden behandeld (niet significant). Er was geen verschil tussen cimetidine en placebo wat betreft het effect van de behandeling op de klachten. De klachtenvermindering bij de patienten die genazen tijdens de cimetidinebehandeling was echter significant beter dan bij de patienten die niet genazen met cimetidine of bij de met placebo behandelde patienten. De maagzuurproductie was niet verschillend bij de patienten die wel en die niet genazen. Het genezingspercentage bereikt met cimetidine werd niet hoger door de duur van de behandeling te verlengen.

Tijdens één jaar onderhoudsbehandeling met 2x400 mg cimetidine per dag kregen 6 van de 7 genezen patienten een recidief oesofagitis.

Geconcludeerd wordt dat de behandeling van ernstige ulcererende reflux oesofagitis met cimetidine bij 50% van de patienten succes had. Maar omdat deze ernstige vorm van oesofagitis de neiging heeft tot recidiveren ondanks onderhoudsbehandeling met cimetidine in een lagere dosering, zal deze behandeling over het algemeen alleen als voorbereiding op meer definitieve (chirurgische) therapie zinvol zijn.

Hoofdstuk 5: De lange termijn behandeling van patienten met het Zollinger-Ellison syndroom met histamine H_2-receptor antagonisten.

Drie patienten met het Zollinger-Ellison syndroom werden gedurende 48, 57 en 60 maanden met histamine H_2-receptor antagonisten behandeld. De behandeling bewerkstelligde een duidelijke vermindering van de maagzuurproductie en een effectieve verlichting van de klachten. Bij één van de patienten moest de cimetidinedosering worden verdubbeld omdat na 15 maanden behandeling de basale maagzuurproductie toenam en opnieuw diarrhee optrad. De behandeling had geen invloed op de nuchtere of de door secretine gestimuleerde serum gastrinespiegels. Bij geen van de 3 patienten werden tijdens de behandeling bijwerkingen geconstateerd.

Hoofdstuk 6: Het effect van één jaar behandeling met cimetidine op de maagzuurproductie, het serum gastrinegehalte en op het zuurremmende effect en de bloedspiegels van cimetidine.

Tweeentwintig patienten met een genezen ulcus duodeni en 16 met een genezen ulcus ventriculi werden gedurende 1 jaar profylactisch met 2x400 mg cimetidine per dag behandeld. De bepaling van de maagzuursecretie bij 20 ulcus duodeni en 13 ulcus ventriculi patienten liet geen verandering zien na 1 jaar behandeling. Bij 11 ulcus duodeni en 6 ulcus ventriculi patienten werd het zuurremmend effect van cimetidine bepaald en bij 9 ulcus duodeni en 4 ulcus ventriculi patienten tevens de bloedspiegels van cimetidine. Ook hierin traden geen veranderingen op na 1 jaar behandeling. Evenmin waren het nuchtere serum gastrinegehalte en de gastrine respons na een testmaaltijd vóór en na 1 jaar behandeling veranderd bij 7 ulcus duodeni en 6 ulcus ventriculi patienten.

Tijdens het jaar behandeling kregen 4 ulcus duodeni en 3 ulcus ventriculi patienten een recidief ulcus. Bij controle gastroscopie na dit jaar werden geen asymptomatische ulcus recidieven gevonden bij de 18 ulcus duodeni en de

13 ulcus ventriculi patienten die onderzocht werden.

De conclusie is dat 1 jaar behandeling met cimetidine geen invloed heeft op het serum gastrinegehalte, noch op de maagzuurproductie of het zuurremmend effect van cimetidine bij patienten met een ulcus duodeni of een ulcus ventriculi.

Hoofdstuk 7: Is het bepalen van de bloedspiegels van cimetidine klinisch van belang?

Bloedspiegels van cimetidine werden gedurende 5 uur na inname van 200 mg cimetidine samen met een proefontbijt gemeten bij 13 ulcus duodeni, 5 ulcus ventriculi en 15 patienten met een anastomose ulcus na een maagresectie. De gemiddelde piek bloedspiegel was 1,14±0,09 µg/ml (uiterste waarden: 0,54-1,94 µg/ml), de gemiddelde tijdsduur dat de bloedspiegel hoger was dan 0,5 µg/ml was 141±14 minuten (uiterste waarden:23-306 min) en de gemiddelde oppervlakte onder de cimetidine bloedspiegelcurve was 166±12 $\mu g.min.ml^{-1}$ (uiterste waarden: 96-280 $\mu g.min.ml^{-1}$). De variatiecoefficient van deze parameters was respectievelijk 33%, 43% en 29%. Er waren geen significante verschillen tussen niet-geopereerde patienten en patienten met een maagresectie wat betreft deze parameters.

Bij patienten bij wie de bloedspiegels tweemaal werden gemeten bleken deze zeer goed reproduceerbaar (correlatiecoefficient >0.90; p<0.001).

Er was geen verschil in piek bloedspiegels, de tijdsduur dat de bloedspiegel hoger was dan 0,5 µg/ml en de oppervlakte onder de cimetidine bloedspiegelcurve tussen de patienten, die na 4 weken behandeling met cimetidine genazen en de patienten die een langere behandelingsduur nodig hadden.

Bij de patienten die een recidief ulcus kregen tijdens profylactische behandeling met cimetidine waren de bloedspiegels ook niet lager dan bij de patienten die geen recidief kregen.

Geconcludeerd wordt dat er grote interindividuele verschillen in cimetidine bloedspiegels bestaan en dat deze verschillen reproduceerbaar zijn. Het bepalen van cimetidine bloedspiegels lijkt echter klinisch niet van belang omdat de hoogte van deze spiegels geen aanwijzing geeft voor de klinische reactie van patienten met een peptisch ulcus op de behandeling met cimetidine.

Hoofdstuk 8: Cimetidine veroorzaakt geen versnelde afstoting van huidtransplantaten bij de muis.

De invloed van cimetidine op de overleving van huidstransplantaten bij de

muis werd bestudeerd in 4 allogene en één xenogene donor-ontvanger combinatie met toenemende histo-incompatibiliteit. Cimetidine, 25 mg/kg, werd om de 8 uur intraperitoneaal toegediend, terwijl controlegroepen met fysiologisch zout werden behandeld. Er was geen verschil in de transplantaatoverleving tussen de met cimetidine behandelde muizen en de controlegroepen.

Hoofdstuk 9: Behandeling met cimetidine heeft geen invloed op immunologische parameters bij de mens.

Bij 9 patienten werden vóór, tijdens en 2 dagen na behandeling met 1,6 g cimetidine per dag een aantal immunologische parameters onderzocht. In vergelijking met 11 controlepersonen werd geen verschil gevonden in de reactie op huidtesten met 5 verschillende antigenen waaronder: candida albicans, bof, trichophyton, PPD en varidase. Het totaal aantal lymfocyten veranderde niet, evenmin als de reactie van lymfocyten in kweek op stimulatie met PHA, pokeweed en een cocktail van de antigenen zoals gebruikt voor de huidtesten. Ook de "mixed lymphocyte cultures" (MLC) en het stimulerend en responderend vermogen van de lymfocyten in de eenzijdige MLC veranderde niet.Het IgG, IgA en IgM gehalte bleef steeds onveranderd normaal.

Hoofdstuk 10: De klinische toepassingsmogelijkheden van cimetidine.

Aan de hand van de literatuur wordt een overzicht gegeven van de verschillende klinische toepassingsmogelijkheden van cimetidine en de bijwerkingen die tot nu toe tijdens het gebruik van cimetidine zijn geconstateerd. Geconcludeerd wordt dat behandeling met cimetidine van het ulcus duodeni, het recidief ulcus na een maagresectie en het Zollinger-Ellison syndroom een duidelijk gunstig effect heeft. Vanwege de onzekerheid over bijwerkingen op langere termijn wordt langdurige behandeling alleen in speciale,daarvoor geselecteerde gevallen geadviseerd. Minder duidelijk is de rol van cimetidine bij de behandeling van het ulcus ventriculi en reflux oesofagitis. Over het voorkómen van stress-ulcera door middel van cimetidine zijn nog onvoldoende gegevens bekend. Tot nu toe zijn vrij weinig bijwerkingen tijdens het gebruik van cimetidine geconstateerd en deze zijn relatief goedaardig. Op dit moment zijn de endocrinologische neveneffecten en de interactie met andere geneesmiddelen het meest van belang, hoewel de klinische consequenties hiervan nog niet volledig zijn vastgesteld. Kortdurende behandeling lijkt zonder risico's.

Allen die aan het tot stand komen van dit proefschrift hebben meegewerkt wil ik oprecht danken.

Het meest ben ik getroffen door de bereidwilligheid die ik steeds opnieuw ondervond bij patienten om deel te nemen aan vaak vervelende en langdurige onderzoeken die voor henzelf dikwijls niet direct tot voordeel waren.

Het laboratorium van de afdeling gastroenterologie heeft een belangrijke rol gespeeld. Dr. Albert Tangerman zette de bloedspiegelbepaling van cimetidine op. Veel van het werk voor deze bepalingen werd door Annie van Schaik verricht. Wil Roeffen verzorgde de serum gastrinebepalingen. Drs. Co Diemel verrichtte een groot gedeelte van de onderzoeken voor hoofdstuk 7.

Het immunologisch onderzoek bij patienten in het kader van dit proefschrift werd verricht in het laboratorium van de afdeling hematologie (hoofd: Dr. J Wessels). Het advies en enthousiasme van Dr. Ben de Pauw waren hierbij onmisbaar. Elly Geestman bracht mij geduldig en nauwgezet de techniek voor de lymfocytenkweken bij, terwijl veel van dit werk niet mogelijk geweest zou zijn zonder de inspirerende hulp van John Smeulders.

De muizenstudie werd gerealiseerd in het dierenlaboratorium (hoofd: Dr. WJI van der Gulden). Dr. Jo Berden maakte mij wegwijs in de transplantatie-immunologie en was de gangmaker van dit onderzoek. Jacqueline Hageman was onovertrefbaar in het transplanteren van de muizen en tevens onmisbaar bij het verdere verloop van dit onderzoek, waaraan ook nog vele andere medewerkers van het laboratorium nefrologie en het dierenlaboratorium hebben meegewerkt.

Pat Mey, de secretaresse van de afdeling gastroenterologie, heeft met de onderzoeken voor dit proefschrift van het begin af aan meegeleefd en vele aspecten meegeorganiseerd. Haar rol is veel groter geweest dan enkel de bereiding van het manuscript en haar ervaring heeft mij erg veel werk bespaard.

De tekeningen werden, soms in bijzonder korte tijd maar steeds met veel zorg, door de heer J Konings van de afdeling medische illustratie vervaardigd.

In geval van nood bleek de mathematisch-statistische adviesafdeling (hoofd: Drs. PH van Elteren) steeds tot hulp bereid.

De verpleegkundigen van de afdeling B50 (hoofd: Zr. Ton van de Belt) en van de endoscopie-afdeling ben ik zeer dankbaar voor hun veelsoortige hulp. Ook de zusters van de polikliniek interne en staf interne ben ik zeer erken-

telijk.

De Engelse tekst werd door de heer JF de Pauw gecorrigeerd.

Tenslotte wil ik mijn collegae bedanken voor het verwijzen van de in aanmerking komende patienten. Mijn collegae van de polikliniek, met name Drs. Ton Cleophas, die geruime tijd een gedeelte van mijn werkzaamheden heeft waargenomen, hebben mij veel ruimte gegeven om een en ander af te werken.

Cimetidine- en placebotabletten werden voor een deel door de firma Smith, Kline & French verstrekt.

De schrijver van dit proefschrift werd op 8 juli 1945 te Tilburg geboren. In 1964 behaalde hij het diploma gymnasium-β aan het St. Willibrorduscollege te Zeist. Daarna studeerde hij geneeskunde aan de Universiteit van Nijmegen en slaagde in 1973 voor het artsexamen.
Hij begon de opleiding tot internist in februari 1974 in het St. Joseph Ziekenhuis te Eindhoven (Dr. FE van Dam, Dr. PFL Deckers, Dr. WMM Driessen en Dr. HAM de Rooy, internisten).
Vanaf december 1975 werd deze opleiding voortgezet in de kliniek voor inwendige ziekten (hoofd: Prof.Dr. CLH Majoor) van het St. Radboudziekenhuis te Nijmegen.
Op 1 februari 1979 werd hij geregistreerd als internist. Momenteel is hij werkzaam op de algemene polikliniek van de universiteitskliniek voor inwendige ziekten (hoofd: Prof.Dr. A van 't Laar) van het St. Radboudziekenhuis te Nijmegen.

STELLINGEN

1 Voor de medicamenteuze behandeling van het ulcus duodeni is cimetidine een goede keus.

2 De behandeling van patienten met het Zollinger-Ellison syndroom met een H_2-receptor antagonist maakt in de meeste gevallen maagoperaties onnodig.

3 Bloedspiegels van cimetidine geven geen indruk over het effekt van de behandeling met dit geneesmiddel.

4 De indicatie tot chirurgische therapie van het ulcus duodeni is door de introductie van cimetidine niet essentieel gewijzigd.

5 Profylactische behandeling met cimetidine van patienten na een niertransplantatie biedt een effectieve bescherming tegen gastro-intestinale bloedingen terwijl deze therapie de transplantaatoverleving niet beinvloedt.
VAN ROERMUND HPC, persoonlijke mededeling

6 Evenals de huisarts dient ook de specialist zich er van bewust te zijn dat hoe meer onderzoek bij een patient wordt verricht des te sterker deze er van overtuigd kan raken aan een somatische aandoening te lijden.
Nascholingscursus voor Huisartsen "Huisarts en Somatische Fixatie", PAOG Nijmegen, 1980

7 Bij zuigelingen met aanhoudende diarree dient een anatomische oorzaak hiervoor te worden uitgesloten.
FESTEN C: Total colonic aganglionosis, a diagnostic problem. Z. Kinderchir. 27: 330, 1979

8 Ondanks het opzienbarende effekt op het gehoor van het plaatsen van trommelvliesbuisjes, levert dit toch geen wezenlijke bijdrage tot de genezing van het glue-ear.
LILDHOLDT T: Unilateral grommet insertion and adenoidectomy in bilateral secretory otitis media: preliminary report of the results in 91 children. Clin Otolaryngology 4: 87, 1979

9 Verwijzing door de arts van zijn patient kan zeer wel, zij het onbewust, tot doel hebben de spanning in de relatie tussen arts en patient te verminderen.

10 Om tot reproduceerbare resultaten te kunnen komen bij het vergelijken van inhalatie-provokatietesten, is het noodzakelijk dat niet alleen de mate van bronchoconstrictie bij de aanvang van het onderzoek maar ook de mate van aspecifieke hyperreactiviteit van de bronchiaalboom vergelijkbaar zijn.

KILLIAN D, COCKCROFT DW, HARGREAVE FE e.a.: Factors in allergen-induced astma: relevance of the intensity of the airways allergic reaction and non-specific bronchial reactivity. Clin Allergy 6: 219, 1976

11 Het optreden van een paradoxale groeihormoonstijging tijdens de orale glucosetolerantietest is in de puberteit een fysiologisch verschijnsel zonder pathologische betekenis.

PIETERS GFFM, SMALS AGH, KLOPPENBORG PWC: J Clin Endocrinol Metab (in press)

12 Als motief voor het in dienst nemen van specialisten in ziekenhuizen worden vaak hoofdzakelijk financiele argumenten aangehaald. Het laten functioneren van specialisten in dienstverband is echter voornamelijk gewenst om redenen van kwaliteit van de gezondheidszorg en van organisatie en beheer van de ziekenhuizen.

Henk Festen
20 juni 1980